

**UKRAINIAN MINISTRY OF HEALTH CARE  
UKRAINIAN ACADEMY OF MEDICINE AND DENTISTRY**

**INTRODUCTION TO CLINICAL MEDICINE (PROPEDEVTIC OF THE  
MEDICINE) WITH PATIENT CARE**

**EDUCATIONAL MATERIALS FOR INDEPENDENT STUDY WITH TESTS  
AND EXPLANATIONS INCLUDED**

**FOR SECOND YEAR DENTAL FACULTY STUDENTS**

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## Preface

Beginning students of medicine and dentistry must acquire a set of skills that prepare them to become clinicians. This includes establishing rapport and a therapeutic relationship with the patient, basic interviewing, the specific conduct and content of medical data collection (the history and the physical examination), formulation of a problem list and diagnostic hypotheses, documentation and record-keeping, and communication with others involved in the patient's care. An introduction to these skills during the first years of medical school focuses on the basics of data collection and information synthesis rather than the specifics of disease, diagnosis, and treatment—that is, the emphasis is on process rather than specialized content.

There are many fine texts that provide detailed discussions of the medical history and physical examination. This instruction is not intended to replace these comprehensive approaches but rather to summarize methods and outline the basic principles essential to data collection.

The authors of this book have all been involved in teaching the Introduction to Clinical Medicine course at the Ukrainian Academy of Medicine and Dentistry. Their experience has informed the **problem based approach** used in this book. This book is structured to allow students to review a set of skills that will enable them to approach undifferentiated medical problems systematically and with confidence in preparation for clinical clerkships.

**I. Kajdashev, M. Rasin**

# Lesson 1

## Physician-Patients Relationship and Professional Deontology

### Basic Components of the Medical History

### Introduction to the Physical Examination

## Physician-Patients Relationship and Professional Deontology

**Adopting a set of values and a professional identity is an important part of a professional education.**

There are many rites of passage that comprise the transformation of a layperson into a medical professional. These involve an increase in knowledge, a change in identity, as well as a familiarity with the events that define the profession (e.g., anatomy and dissection of the human body, access to intimate information about patients, and performance of invasive procedures).

**1. Intimate information.** Patients often share intimate information with clinicians about family difficulties, sexual relationships, and fears about disability and death. It is important that student-clinicians develop strategies for responding appropriately to the patient's needs as well as their own.

**2. Lack of legitimacy.** Students often feel that they are somehow just "playing" at being clinicians and that the patients with whom they work might just as well share intimate information; the person in the next bed. This is often compounded by "looking young" and having patients question their role as student-clinicians. This is one of the most difficult rites of passage in becoming a clinician. Students can manage these situations by:

- a. Explaining their stage of training and level of responsibility-for example, "I am a medical student, and I am here to interview you as part of our medical history course.
- b. Developing confidence about data collection skills and an awareness that new important information may be discovered.

**3. Conflict between education and patient care.** Some students feel a tension between educational objective and providing patient care. They are often concerned that they "using patients" when they repeat examinations that are clinically unnecessary.

However students should not overlook the fact that:

- a. They may discover something new and important.
  - b. Most patients are pleased that they have something worthwhile to teach students.
- Many patients appreciate the extra attention and benefit from the additional time that students spend listening to their histories.

**4. Patients with self-inflicted problems.** Frequently, clinicians encounter patients who have acquired diseases or disabilities from high-risk behaviors, such as alcohol abuse, resulting in liver failure; heavy cigarette consumption, resulting in emphysema or lung

cancer; and intravenous drug use, resulting in endocarditis, osteomyelitis, or acquired immune deficiency (AIDS). While these patients may engender feelings of anger or frustration in health professionals, they still require sensitive and medically appropriate care.

**5. Patients with terminal illness.** Student-clinicians must explore their feelings about dying so that they can better attend to terminally ill patients and their families. The commonest reactions to death and dying are:

- a. Withdrawal from the patient to avoid emotional involvement or sadness about impending loss
- b. Anger over "treatment failure"
- c. Feelings of inadequacy in caring for the patient
- d. Denial

**2. Distancing.** Stepping aside and trying to view a given situation objectively can provide perspective. Distancing is an important coping strategy, which medical students must acquire early, so that they can analyze their interactions with patients, peers, and preceptors.

**3. Self-control.** Learning to control immediate emotional reactions is important for functioning well in clinical encounters. Although the immediate emotional response to a situation may not be appropriate to communicate to the patient, it should always be analyzed and discussed (see I E 1, 4).

**4. Seeking social support.** Developing support systems is important so that the student-clinician does not feel completely isolated and can engage help during the stressful periods of medical education.

**5. Positive reappraisal.** Reframing a stressful situation to determine the areas of learning is another positive strategy.

**6. Confrontation.** Examining the causes of discomfort or seeking clarification from faculty about areas of conflict can help students to deal positively with stress. Students often need to learn how to approach confrontation in an assertive rather than aggressive way. While many students chose medicine because of a desire to work with people, they often feel more isolated in the first 2 years than at any other point in their lives.

## **2. CONFIDENTIALITY**

**A. Definition.** All communication between patient and clinician is privileged and legally protected. Without the written consent of the patient, this information may be shared only with individuals who are involved in the patient's care.

**B. Maintenance of confidentiality.** Confidentiality is one of the key elements of the profession of medicine and the delivery of health care.

**1. Use of initials or anonymity.** To preserve confidentiality, it is standard practice to use either initials or general descriptors (e.g., L. K. is a 55-year-old female Caucasian postal worker with a 10-year history of hypertension) in the presentation of case information.

**2. Professional exchange of information.** It is standard and appropriate practice that

information obtained from the patient may be shared with other health professionals under specific circumstances.

**a. Patient care.** Other professionals involved in the ongoing care of patients may need to know information collected from the patient by another professional. In this instance, the name of the patient is necessarily used.

**b. Educational purposes.** When patients agree to participate in an educational activity, confidentiality should be maintained in any verbal or written presentation, using initials or general descriptors as described above.

**3. Patient's family and friends.** Information collected from patients should not be shared with their family or friends unless the patient indicates that this is acceptable. A demand from a family member to know, about drug use or sexual behavior of an adolescent child or a spouse is a social example of the type of conflict that may occur.

**PATIENT PERSPECTIVE.** To provide appropriate care, clinicians must have an understanding of the perspective patients bring to the health care encounter.

**A. Social context.** Patients and clinicians are influenced by and act on the expectations of the society of which they are a part.

**1. Sick role.** In 1951, Parsons, a sociologist, developed a theoretical perspective on the functional meaning of being sick in Western societies. From his perspective, illness is a socially undesirable state, which prevents a person from performing ordinary tasks and roles and which must be remediated as soon as possible. There are four major components to the sick role, two "rights" and two "duties."

**a. Rights of the sick role**

- (1) Recognition that the sick person is not responsible for his or her state and, therefore, cannot be blamed
- (2) Exemption from work obligations and normal social responsibilities

**b. Duties of the sick role**

- (1) Obligation to "want to get well" and, therefore, cooperation in any therapeutic effort
- (2) Obligation to seek competent and appropriate treatment

**2. Illness response factors.** The decision to seek medical care usually involves the patient's attempts to act on symptoms and health concerns in accordance with the obligations discussed in the sick role.

a. Patients must first make sense of the problem and define it within the constraints of their cognitive ability and social and cultural milieu.

b. The patient's definition of illness and treatment may not be compatible with that of the clinician, and this discrepancy may result in considerable miscommunication between the clinician and the patient.

c. Mechanic (1968) defined several dimensions within which the patient determines the importance of acting upon an illness.

- (1) Visibility, recognizability, or perceived immediacy of signs and symptoms
- (2) Perceived seriousness of symptoms; that is, the patient's estimate of the present and

future likelihood of danger

- (3) Extent of disruption of normal activities, involving family, work, and other social activities
- (4) Frequency of symptoms or episodes of illness
- (5) Tolerance to symptoms of patients, their families, and the social environment
- (6) Knowledge, understanding, and cultural assumptions about the signs and symptoms
- (7) Basic needs competing with illness responses or affecting perception of symptoms
- (8) Competing explanations for symptoms
- (9) Availability of treatment resources, distance to treatment, and psychological and monetary costs of taking action

**B. Disease factors.** Once a disease has been diagnosed, there are aspects of the condition that influence how a patient responds to clinicians in the health care encounter, including the duration and severity of the condition as well as the effectiveness of available treatment.

**1. Acute disease.** Diseases that are self-limited or that can be easily diagnosed and treated are usually easier for the clinician and patient to manage.

- a. Data collection involves events with a short chronology, making it easier for students to organize questions and responses.
- b. While patients may be anxious about the presenting symptoms, the short duration aids in presenting the chronology and usually enhances the validity of information.
- c. There will be little or no history of contact with other clinicians regarding the present condition.

**2. Chronic disease.** Chronic diseases may present problems for both clinicians and patients in terms of remembering the chronology of the illness, effective management, or compliance with treatment. Students may have difficulty keeping track of a long history, which may irritate some patients. b. Patients with chronic disease often have a history of previous encounters with clinicians, some of which may have been negative, thus influencing the present interaction. c. Clinicians should try to get some sense of the patient's previous experience with the health

Care system.

**3. Serious or terminal illness** may cause considerable discomfort for clinicians, and patients are extremely sensitive as to how issues are explored and handled. Patients are also concerned with how clinicians deal with emotional and family matters.

and given a choice.

**2. Family issues.** The family should be informed of the level of training and the responsibility of those involved in the care of the patient.

**3. Home setting.** Home visits by clinicians, although rare, can provide invaluable information for patient care. They present a good opportunity to see how the individual functions outside the medical environment.

**D. Patient as teacher.** A basic tenet of the physician-patient relationship is that the patient is always a teacher—that is, it is the patient who experiences the illness and, therefore, has the most information about the symptoms and their impact on daily life.

**C. Limitations.** Two exceptions to the rule of confidentiality concern the professional responsibility of clinicians and student-clinicians to guard the safety and well-being of the patient and

1. When patient threatens suicide or other immediately self-destructive behavior, clinician has a responsibility to intervene.
2. When patients threaten to harm others, clinicians have a responsibility to take action.

**A. Touching—a professional issue.** Touching of strangers is an act laden with cultural interpretation that must be carefully considered by individuals embarking on a career in which it is mandated. Parish reminds us that "Medicine is a delicate blend of science and art. The clinical approach may, on occasion, be the patient's only source of hope. To touch or lay on may convey human warmth, perhaps even an act of compassion. Touching can be a therapeutic measure, especially when utilized in diseases of less than certain origin. Exploration of the ways in which touching becomes a part of the professional role is part of student's education.

**1. Concept of personal space.** Each individual has personal views of the concept of space, which is established very early in life. It is essential to understand and to recognize differences among individuals in connection with this concept.

**2. Fear of touching.** Concerns about touching can be overcome by developing an understanding of the value of touching, as well as its boundaries. Fear of touching may be the result of a. The clinician's background or sense of personal space b. Fear of sexual arousal c. Concern that the patient might not want to be touched

**3. Fear of being touched.** Some patients fear being touched, perhaps as a result of being a clinician's touch or perhaps because they are stridently protective of personal space. Patient's feelings about being touched should be anticipated, using a "sixth sense" developed with time and experience.

## **B. Types of touching**

**1. Diagnostic touch.** It is impossible to conduct a physical examination without direct contact.

a. After the initial introduction and handshaking, the least intrusive parts of the examination such as taking a pulse or blood pressure, are a good introduction to crossing the personal space barrier. Warm hands and a gentle approach, maintaining conversation and explaining each step, help to relax the patient about being touched. b. Patients should be warned before being touched deeply, as in an abdominal examination.

**b. Getting permission.** Permission should be obtained before doing something that will be unpleasant or painful. This "contract," or agreement, gives the patient a sense of control and is essential for the successful accomplishment of the mutual goal of the patient and clinician. **3. Healing touch.** From the initial handshake of greeting to the final resolution of the medical problem, the method of touching is a part of the relationship. If the patient is in distress, a touch on the hand conveys understanding and empathy.

Sometimes patients need a hug or need to have their hand held in sympathy. Learning how much of the clinician's touch is healing, and when it becomes harmful to the professional relationship, requires constant reassessment.

**V. LANGUAGE. Clinical language is full of abbreviations, jargon, and anatomic terms used to describe data collection and diagnosis, which can intimidate the student.**

#### **A. Basic definitions**

**1. Symptoms** are any problems experienced by the patient that may be related to a health condition. Symptoms usually are used to identify the underlying pathology.

**2. Signs** are physical indications of the disease or syndrome. They may be visible to anyone or specifically to the clinician in the course of the examination.

**3. Diagnosis** is a determination of the underlying cause of a symptom or sign or set of symptoms or signs. **4. Prognosis** is the predicted course of a disease-that is, its duration, progression, and outcome.

**5. Genogram** is a diagram of a family tree with specific reference to health conditions.

**6. Activities of daily living (ADLs)** are a measure of a patient's level of functioning. They can be used to assess the function levels of all patients, but they are most often used to evaluate chronically ill and geriatric patients.

#### **C. Sensitivity of words and labels**

**1.** The phrase, "patient denies alcohol use" or "denies any history of. .." implies that the patient is not telling the complete truth. While many clinicians use this phraseology, there are other nonjudgmental *ways* of describing the patient's behavior, such as "the patient reports, states, or indicates."

**2.** Negative or implied responsibility is also inherent in certain medical diagnoses, such as "incompetent" cervix, which can easily be misunderstood by the patient, although it is standard medical usage. Such terms should be discussed with the patient to ensure that there is no implication of judging the patient or the condition.

**3.** Precise information and avoidance of labeling is also important in describing patient behaviors. Thus, it is more precise to say "The patient reports consuming 6 beers each day" rather than "The patient is an alcoholic."

### **Basic Components of the Medical History**

**I. COMPONENTS OF THE COMPREHENSIVE MEDICAL HISTORY.** The medical history is the foundation upon which diagnosis and treatment are made. It is the basis upon which hypotheses are built and tests ordered. Without a medical history, the clinician works in a vacuum. The medical history provides a place for the establishment of the physician-patient relationship; at the time of the history, rapport is created and trust begins.

**Chief components of medical history are:**

**A. Chief complaint.**

**B. Identifying dates (Passport dates).**

**C. History of present illness (HPI) (Anamnesis morbi).**

**D. Review of systems (ROS).**

**E. Past medical history (PMH) (Anamnesis vitae).**

### **A. Chief complaint (CC)**

**1. Definition and elicitation.** The medical history usually begins with a determination of the patient's CC, which is the patient's perception of the problem or symptom for which he or she has sought a health care provider.

a. The CC is usually elicited immediately after introductions by asking one of the following questions; for example, "What brought you here today?" "What problem brought you to the hospital?" "What symptoms cause your distress?"

b. Patients often give short, succinct responses, such as, "I had chest pain," or "My diabetes was out of control."

**3. Recording.** The CC is described in both the written history and the oral presentation by using the patient's exact words: "I fell over the curb and broke my leg." The clinician *mustn't* paraphrase the CC and write "broken leg."

**4. Relationship to other problems.** In most cases, the CC gives the clinician a clear understanding of the patient's major concern. However, the clinician may discover from the history or the physical examination that the patient has another or more serious medical problem. For example, the patient's CC may be "My knee has been hurting," but on examination, the clinician may find that the patient has asymptomatic hypertension. This does not alter the CC. The clinician must deal with the hypertension as well as the painful knee.

### **B. Identifying dates (Passport dates)**

#### **1. Definition and recording**

a. Identifying data give the reader or listener a mental picture of the patient, including the name, age, sex, and occupation, eventually leading to the CC. Some clinicians also include the number of admissions to the hospital. Examples follow: (1) Mr. Young is a 59-year-old steelworker with the CC: "I need another operation on my hand."

(2) This is the seventh hospital admission for Mr. Young, a 59-year-old steelworker with the CC: "I need another operation on my hand."

b. **Ethnicity** is not included in the identifying data unless this information is essential to the diagnosis; for example, certain diseases are more prevalent in certain racial or ethnic groups, such as sickle cell disease in blacks. In this instance, the clinician might write, James Foster is a 5-year-old black child with the CC: "My fingers hurt."

#### **2. Supplementary content**

- a. Identifying data can also include medical facts that influence the remainder of the medical history (especially the history of the present illness); for example:
  - (1) Knowing that a patient has diabetes may alter the treatment; for example, Mrs. O'Connor is a 59-year-old accountant with a 40-year history of insulin-dependent diabetes mellitus (IDDM) who comes into the hospital with the CC: "I have a sore on my foot."
  - (2) A fever may be much more significant in a patient on chemotherapy than in a healthy individual; for example, Mr. Bradley is a 67-year-old, retired salesperson who is currently receiving chemotherapy at home and now comes to the hospital with the CC: "I have a fever."
- b. Reliability of the patient is assessed throughout the history. This judgment is based upon the patient's recall and reproducibility of facts rather than the interviewer's inexperience or lack of ability in obtaining data.
- c. Third-party informant. If someone besides the patient contributed to the history, it should be noted as: Informant-patient's wife who had minimal recall of events before 1987.

## C. History of present illness (HPI) (Anamnesis morbi)

### 1. Overview

a. **Patient's description of symptoms.** The HPI should include only symptoms—that is, information that the patient reports about changes in function, appearance, or sensation. A symptom is a subjective description. The HPI should not include signs, which are any abnormalities discovered by the clinician on direct observation or examination—that is, an objective indicator. The student may ask the patient about symptoms concerning something that he has observed (a sign): "I notice that your fingers do not move. Could you tell me about that?" In the HPI, the clinician reports **only the symptoms that the patient describes**. Objective descriptions are part of the physical examination.

### b. Acquiring primary data

(1) Primary information. The student should investigate the patient's primary symptoms rather than accept third-hand information as fact. For example, if the patient reports,

*"The doctors said I have a gallbladder problem,"* the student must obtain a complete history. *Only primary information belongs in the history.*

(2) **Secondary information** is data obtained from sources other than the patient, such as laboratory values or old records.

(3) **Tertiary information** is information related verbally by the patient as if it had come from another source, such as, *"My doctor told me I have gallbladder disease."*

c. **Nonjudgmental attitude.** The history should not reflect a bias. It should be obtained in a manner that does not impose the interviewer's values, beliefs, or prejudices about the patient or his problem. The phraseology of the questions can have a marked influence on the patient's response; for example, "You have never had venereal disease, have you?" A patient questioned this way is unlikely to say "Yes." In sensitive areas,

such as the alcohol, drug, or sexual history, the clinician frequently will inadvertently slant the questions, make assumptions, and fail to ask pertinent questions. Examples include:

(1) The clinician assumes that a married woman has only one sexual partner and fails to ask about sexually transmitted diseases.

(2) The clinician assumes that a patient over 80 years of age cannot give an accurate history.

**d. Presence of third party.** Occasionally, a patient's spouse, child, or friend is present during the interview. This individual can add information or remind the patient of dates or the chronology of a problem.

(1) The clinician must be careful not to direct all questions to a third party, since the history should be the patient's view of the problem.

(2) It may be difficult to ask sensitive questions in the presence of another individual.

These questions can be deferred or posed during the physical examination, when the clinician is alone with the patient.

(3) If the third party is not a close family member or intimate friend, it is appropriate to ask the visitor to leave while the history and physical examination are conducted. (4) The patient's preference should guide the interviewer in the decision to allow a third party to be present during the acquisition of the history.

**e. Unreliable patients.** The patient's inability to remember facts or to give a consistent story should be documented. Old records and interviews of the patient's family or friends may be necessary to acquire complete and reliable information.

**2. Seven parameters of each symptom** are needed to complete the HPI (see a-g below). Often asking the patient an open-ended question, such as, "Take me from the time you noticed the back pain until today and describe what happened," will provide the clinician with most of the parameters. Details can then be obtained by asking additional questions.

**a. Chronology** of the symptom from the time it first started to the present time must be determined.

(1) The chronology of an **acute symptom**, such as dysuria, may only encompass a few days.

(a) Within that time, the pattern, severity, and any changes in the symptom should be described. Asking an open-ended question, such as, "Take me from the first time you felt the pain, and tell me what has happened since," will often provide the needed information.

(b) The clinician must ascertain if an acute symptom has ever occurred before.

(2) The chronology of a **chronic symptom** can span decades, such as diabetes or intermittent back pain for 10 years. The emphasis should not be on a day-to-day description of the problem but a gestalt of the disease over the years; for example, "The patient was

asymptomatic until approximately 12 years ago when increased blood sugar was discovered on routine screening. The patient did well on diet and exercise without medication until approximately 5 years ago when symptoms of polyuria, polydipsia, and polyphagia occurred. The patient is regulated on 20 units NPH insulin and has been stable without complications or hospitalization until now."

(3) An **acute exacerbation** of a problem should be described first (using the parameters listed below). The clinician then goes back to the onset of the problem and describes the entire chronology up to the acute event.

**b. Quality.** The quality of a symptom is a detailed description of what exactly the symptom is.

(1) Vague terms, or terms that have different meanings for different people, such as dizziness or diarrhea, should be clarified.

(2) As many adjectives as possible should be used to describe the symptom; for example, "Sudden, sharp, knife-like chest pain," or "Hacking cough with about a teaspoon of greenish phlegm, which prevents sleep at night" are clearly descriptive.

(3) Analogies to describe the symptom can be helpful, such as, "Heavy pain like an elephant sitting on my chest."

**c. Quantity** of a symptom is the magnitude or intensity.

(1) A common mistake is to take the patient's "a lot" or "not much" as sufficient. These terms are too vague and often misleading.

(2) It helps to quantify a symptom by relating it to the person's activities of daily living (ADLs); for example, "Shortness of breath has increased so that the patient can now climb only five steps without stopping," or "Pain keeps the patient from sleeping."

(3) Some interviewers ask patients to rate the symptom of pain on a scale from 1 to 10, which works if the scale is defined. If the patient says the pain was an "8 out of 10," and "10" was natural childbirth, that tells the clinician a great deal. On the other hand, if the patient has no context for a "10," then saying the pain was an "8" is not a helpful quantification.

(4) It is necessary to quantify any symptom throughout its chronology; for example, "The loose stools occurred only once a day for 3 days, then increased to four to five times a day for a week, and now are occurring about every 4 hours."

(5) The chronology of a chronic disease should be carefully documented; for example, "The knee pain began 5 years ago. Initially the pain only occurred when the patient had to torque the right knee when playing sports. Gradually, about 3 years ago, the patient began to get pain when climbing up and down stairs and doing minimal activity, such as mowing the lawn, but the pain ceased when the patient stopped the activity. The frequency of the pain has increased in the past 3 months so that the patient experiences it when walking about one-quarter mile, and it no longer goes away with the cessation of activity."

**d. Location.** It is important that the patient identify where the symptom is located.

(1) The patient may point to a particular place but use incorrect **anatomic** ample, he or she may point to the left lower quadrant of the abdomen stomach pains." It is the clinician's job to interpret this correctly.

(2) It is important to learn:

- (a) If the symptom radiated anywhere
- (b) If the symptom is generalized or can be pinpointed to one **part**
- (c) If touching or other maneuver of the area produces the symptom.

**e. Setting** is the context in which the symptom occurs.

(1) It is important to know that the abdominal pain occurred 2 hours after foods, that a patient who is allergic to cats had difficulty breathing M of entering a house with two cats, or that a patient has chest pain after p

(2) The setting also includes information, such as:

(a) Contact with other people who have the same symptoms (i.e., all th house have the same rash)

(b) Travel to areas where such symptoms are known to be endemic (ia returned from Mexico where symptoms began)

(c) Occupational risks (i.e., symptoms occur only on work days)

(3) Any factor that may affect how or when the symptom occurs must be s

**f. Alleviating and aggravating factors** include any activity, event, or attempted makes the symptom better or worse; for example, "The swelling went away two hours after elevating the leg," or "Walking on a cold winter day made my breath worse."

(1) If any medication has been tried, its effectiveness should be determined; fc "I tried two extra strength aspirin (ASA) for the headache without relief." pain stopped 2 minutes after using nitroglycerine."

(2) Open-ended questions may expedite a full answer; for example, "Did any tried make the itching better?" Patients may, however, not be conscious of cifically helped or did not help.

(3) As students learn more medicine, they will be able to ask specific **question!** ended questions are not helpful. Specific questions may help the patient rec event and provide positive or pertinent negative responses.

**g. Associated symptoms** are other symptoms that occur with or during the course of 1 problem being described. For example, the patient may have had a cough for 2 days developed a fever of 102° F on day 3. The fever may be construed as a symptom a' (in time) with the cough.

(1) It is often difficult to ascertain whether or not associated symptoms are pat ologically related; for example, in a patient with burning on urination why develops a vaginal discharge and lower back pain, the clinician may mine whether the latter two symptoms are related to the dysuria or whether they to be developed individually.

(2) Novice interviewers should separate the problems unless they feel confident i them together. As students learn more about the constellation of symptoms t prise certain illnesses, decisions will become easier; for example, once stuc derstand diabetes mellitus, they will consider weight loss, polyuria, and poly symptoms related to a single disease process.

**h. Complications.** Predictable complications of any extant chronic disease should b~ although they are not considered one of the seven parameters. Some complications are serious and may need to be presented separately; for example, a patient may have; failure as a complication of diabetes mellitus.

**i. Summary.** After all seven parameters have been covered by the clinician, it is helpful summarize the information that has been obtained.

(1) This provides an opportunity for both clinician and patient to check the information for completeness and accuracy.

(2) Additional questions may be asked once the summary has been completed

j. If the patient is loquacious, the clinician may instruct him or her to wait until the interview

is completed to clarify or correct any information.

### **3. Patient's perception of causality**

a. Asking patients if they have any preconceived ideas about what is causing the problem be enlightening. A patient complaining of headaches may fear a brain tumor.

b. Patients may have concerns or phobias that need to be addressed; for example, a 50-year-old patient may believe that a heart attack is imminent if one or both parents died from heart attacks when they were 50 years of age.

c. Asking patients if there is anything they wish to add that has not already been covered may provide additional information about which the patient may not have felt comfortable discussing earlier.

### **4. Multiproblem HPIs.** Patients can have multiple concurrent symptoms or problems.

a. Any problem or symptom for which patients are currently being treated should be included in the HPI. The HPI of the patient with a presenting complaint of "shortness of breath" who also has arthritis and diabetes should list each of the three problems separately in the HPI with the seven parameters determined for each.

b. Problems that occurred in the past, have been resolved, and have no impact on the patient today belong in the past medical history.

**5. Controlling the interview.** The greatest difficulty for most interviewers is directing the interview so that the patient talks about each problem separately. One tactic that can be used when a patient deviates from his shortness of breath to his abdominal pain is to say, "I am very interested in the abdominal pain, but let us finish discussing shortness of breath first and then you can tell me all about your abdominal pain." The clinician should then return to the abdominal pain: "You mentioned abdominal pain earlier; could you tell me about it now?"

## **G. Review of systems (ROS)**

**1. Definition and elicitation.** The ROS is the final part of the history. Its purpose is to determine that no major problems have been missed.

a. To avoid hearing about every cold or case of hemorrhoids during a pregnancy 15 years ago, specific guidelines are given to the patient as part of the introduction, such as, "I am interested in knowing about any unusual problems in the last year." There are, however, patients who, despite instructions, relate minor past problems in great detail and must be redirected.

b. It is important to let the patient know that, unlike the prior parts of the history, the ROS will be acquired by means of multiple closed-ended ("yes" or "no") questions.

c. Occasionally, the ROS will identify another problem for which the seven parameters must be pursued.

**2. Specific components.** The following list is a sample of a typical ROS. The clinician asks these questions in a language that the patient will understand-that is, "difficulty breathing" rather than "dyspnea." If the interviewer does not know the medical significance of a positive response, he may need to acquire the full seven parameters.

**a. General.** Usual weight, recent weight change, weakness, fatigue, and fever

**b. Skin.** Rashes, lumps, itching, dryness, color change, and changes in hair or nails

**c. Head.** Headache and head injury

**d. Eyes.** Vision, glasses or contact lenses, last eye examination, pain, redness, excessive tearing, double vision, glaucoma, and cataracts

**e. Ears.** Hearing, tinnitus, vertigo, earaches, infection, and discharge

**f. Nose and sinuses.** Frequent colds, nasal stuffiness, hay fever, nosebleeds, and sinus trouble

**g. Mouth and throat.** Condition of teeth and gums, bleeding gums, last dental examination, sore tongue, frequent sore throats, and hoarseness

**h. Neck.** Lumps in neck, "swollen glands," goiter, and pain in the neck

**i. Breasts.** Lumps, pain, nipple discharge, self-examination, and data from last mammogram

**j. Respiratory.** Cough, sputum (color and quantity), hemoptysis, wheezing, asthma, bronchitis, emphysema, pneumonia, tuberculosis, pleurisy, tuberculin test, and last chest x-ray

**k. Cardiac.** Hearttrouble, high blood pressure, rheumatic fever, heart murmurs; dyspnea, or thopnea, paroxysmal nocturnal dyspnea, edema; chest pain, palpitations; and past electrocardiogram (EKG) or other heart tests

**l. Gastrointestinal.** Trouble swallowing, heartburn, appetite, nausea, vomiting, vomiting blood, indigestion, frequency of bowel movements, change in bowel habits, rectal bleeding or black tarry stools, constipation, diarrhea, abdominal pain, food intolerance, excessive belching or passing of gas, hemorrhoids; jaundice, liver or gallbladder trouble, and hepatitis

**m. Urinary.** Frequency of urination, polyuria, nocturia, dysuria, hematuria, urgency,

hesitancy, incontinence, urinary infections, and stones

#### **n. Genitoreproductive**

**(1) Male.** Discharge from or sores on penis, history of venereal disease and its treatment, hernias, testicular pain or masses; and frequency of intercourse,\* libido, and sexual difficulties

#### **(2) Female**

**(a)** Age of menarche; regularity, frequency, and duration of periods; amount of bleeding, bleeding between periods or after intercourse, or last menstrual period; dysmenorrhea; and age of menopause, menopausal symptoms, or postmenopausal bleeding

**(b)** Discharge, itching, venereal disease and its treatment; and last Pap smear.

**(c)** Number of pregnancies, deliveries, and abortions (spontaneous and induced); complications of pregnancy; birth control methods; and frequency of intercourse,\* libido, and sexual difficulties

**o. Musculoskeletal.** Joint pains or stiffness, arthritis, gout, and backache (if present, describe location and symptoms, such as swelling, redness, pain, stiffness, weakness, and limitation of motion or activity); and muscle pains or cramps

**p. Peripheral vascular.** Intermittent claudication, cramps, varicose veins, and thrombophlebitis

**q. Neurologic.** Fainting, blackouts, seizures, paralysis, local weakness, numbness, tingling, tremors, and memory

**r. Psychiatric.** Nervousness, tension, mood, and depression

**s. Endocrine.** Thyroid trouble, heat or cold intolerance, excessive sweating, diabetes, and excessive thirst, hunger, or urination

**t. Hematologic.** Anemia, easy bruising or bleeding, past transfusions, and possible reactions

### **E. Past medical history (PMH) (Anamnesis vitae)**

**1. Definition and significance.** The PMH is obtained to ascertain any medical information from the patient's past that may have an impact on the present or future. The patient should be told that the interviewer plans to focus on major health problems. Clinicians should provide guidelines to direct the patient toward their agenda, which must be met in the PMH.

#### **2. Content**

##### **a. Childhood illnesses**

**(1)** The questions vary depending upon the age of the patient. For example, knowing that

a 5-year-old child has had chicken pox is relevant. Learning if a woman in her child-bearing years has been vaccinated against rubella is important, but this same information is less crucial in a 78-year-old woman.

(2) Major childhood problems should be reviewed. To trigger a patient's memory, the interviewer may ask if the patient stayed home from school for long periods of time or was hospitalized during childhood.

(3) With elderly patients, illnesses that have continued from childhood into adulthood (e.g., asthma) are important. Spending time determining whether or not a 70-year-old person had measles or mumps is not useful.

**b. Adult illnesses.** This includes problems that have been resolved and are not currently causing any symptoms nor being treated in any way (i.e., by medication or diet).

(1) A potential pitfall for students is their tendency to lump all of the patient's problems, other than those related to the CC, into the PMH.

(2) There are two major hazards in following this format:

(a) The clinician is responsible for being aware of all the patient's problems. For example, although the patient may be in the hospital for a total hip replacement, the clinician cannot ignore COPD and diabetes, which need constant monitoring and medication.

(b) Problems may be interrelated; for example, in the patient with diabetes who is admitted for total hip replacement, the glucose level, amount of insulin needed, and type of intravenous fluids are affected by the stress of surgery and the recovery period.

(3) Problems that do belong in the PMH include:

(a) Tuberculosis treated in 1964 with isoniazid (INH), streptomycin, and para-aminosalicylic acid (PAS) for 2 years with no sequelae. The last chest x-ray in 1984 was reported as "unchanged since 1979."

(b) Asthma attacks two to three times a year until age 25 with no symptoms since

**c. Surgical procedures.** The following information should be obtained about all surgical procedures:

(1) **Date of surgery** or, if not known, approximate age of patient at time of surgery

(2) **Place of surgery**, especially for recent surgeries and those related to any current problems

(3) **Reason for surgery**, which is obvious in some cases (e.g., appendectomy) but less so with others (e.g., hysterectomy). The symptoms that led to the operation should be determined.

(4) **Sequelae.** Any complications during or after surgery should be determined.

**d. Accidents and injuries**

(1) Accidents, their causes, and all medical problems relevant to the accident should be listed with any sequelae; for example, a fall from a tree while playing that resulted in a fractured tibia or a car accident that resulted in headaches for 3 weeks.

(2) Occasionally, there is a repetitive nature to these accidents. Clinicians should be attuned to the possibility of physical abuse or substance use and ask appropriate questions.

**b. Occupation.** Assess the type of work, current and past employment, stress levels, and effect of illness on job status. Ask about health insurance and the potential financial impact of this illness.

**d. Activities of Daily Livings (ADLs).** Clinicians should attempt to learn what, besides

work, patients do—that is, to which hobbies or organizations are they attracted. Clinicians may also ask about habits, such as exercise, diet, alcohol, cigarettes, and recreational drugs.

**e. Patient concerns.** Any concerns, fears, anxieties (whether or not related to the illness) should also be elicited, such as fear of divorce, concern about a diagnosis, or grief surrounding a recent loss.

#### **f. Immunizations**

(1) The type of information to be acquired is age-dependent. Immunization for many of the childhood communicable diseases is relatively recent; therefore, it is not relevant to the history of an elderly patient.

(2) Until the student is conversant with all the vaccines and ages at which they should be given, it is probably safe to ask mothers of young patients if their "shots" are up-to-date and whether they had any problems with immunizations.

(3) The clinician should ask adults about the date of the latest tetanus shot.

(4) Elderly patients and any adult or child with chronic medical problems should be asked about pneumonia and influenza immunization.

**g. Obstetric history.** Although most interviewers would not expect the obstetric history to be a sensitive or emotional part of the overall history, sometimes sad memories are relived. Acknowledgment or other personal response can be helpful. Regardless of the marital status of the patient, the clinician should inquire about the following: (1) Number of pregnancies (gravida)

(2) Number of live births

(3) Number of abortions, either spontaneous or induced

(4) Types of delivery, either vaginal delivery or cesarean section

(5) Problems with pregnancies, such as high blood pressure, placenta previa, or premature birth

(6) Sequelae, such as postdelivery hemorrhage

**h. Psychiatric history.** There is still a stigma associated with seeing a psychiatrist.

(1) Nonjudgmental ways of asking about a psychiatric history are: "Have you ever seen, or felt the need to see, a counselor or psychiatrist?" "Have you ever been hospitalized for an emotional problem?"

(2) If the patient has a serious, debilitating, or fatal disease, the clinician may also open up the potential need for counseling by saying, "It must be very difficult to be so young with a disease like lupus; do you think it would help to talk with someone?" (3) These same questions, if indicated, could be asked during the HPI or the PP.

**i. Medications.** Many people take medications without knowing their names or why they were prescribed; therefore, it is important to ask for the following information: (1)

#### **Current prescribed medications**

(a) Names

(b) Doses

(c) Reasons for use

(2) **Nonprescription medications.** Any over-the-counter medication (i.e., analgesics,

antacids, or antihistamines) may cause problems for individual patients. For example, certain antihistamines interact with blood pressure medication; ASA may alter the effect of warfarin; some sodium-containing antacids may complicate congestive heart failure (CHF).

**Recreational (illicit) drug use** must be explored with all patients in a nonjudgmental manner. No assumptions should be made on the basis of the patient's age or economic and social position.

### **Health habits**

**(1) Exercise.** Any formal or regular exercise or sports should be noted.

**(2) Diet.** Information is most easily obtained by asking the patient to describe what was eaten on a particular day. (For more in-depth dietary history, see Chapter 4 V.) **Alcohol** is such a prevalent and accepted part of our society that the clinician may ask, "During an average week, how much beer, wine, or hard liquor do you drink?" Patients often give vague answers, such as "I only drink socially," or "I drink no more than usual." These answers are inadequate. It is the clinician's responsibility to elicit a more detailed history. At times, it may help to overestimate the amount consumed and let the patient make corrections. The clinician should learn what type of alcohol and how much is consumed each day or week (see Chapter 4 III).

### **(4) Tobacco**

**(a)** All patients should be asked if they smoke cigarettes, cigars, or a pipe. Clinicians must also determine how much tobacco is smoked and for what duration. Cigarette consumption is usually recorded as the number of packs smoked each year (pack/years).

**(b)** Often people who have smoked two to three packs a day for 20 or more years and stopped recently deny smoking unless asked about past smoking history. Thus, the past smoking history should be obtained, including the date of cessation.

### **k. Allergies**

**(1) Medication.** Patients should be asked if they are allergic to any medication.

**(a)** Patients must be asked specifically what happens when the medication is taken. This will help the clinician to differentiate a true allergic response from an adverse reaction, such as an upset stomach with some antibiotics. This information may become crucial if the patient should need a particular medication. The clinician may choose to deal with the patient's "upset stomach" and give the needed antibiotic but would not opt for that antibiotic if the patient had a history of difficulty breathing, which required epinephrine.

**(b) Penicillin allergies** are common; therefore, patients should be asked about this particular medication.

**(2) Foods.** The patient must be asked about any food allergies.

**(a)** This will avert problems in ordering a hospitalized patient's diet.

**(b)** It will avert prescribing certain medications, which may be made from the allergic product, such as porcine insulin in the pork-allergic patient.

**Other.** Seasonal allergies, bee-sting reactions, and animal dander allergies should all be elicited and information obtained about the symptoms of the reaction.

## **F. Family history (FH)**

**1. Definition and elicitation.** The FH gives clues to familial or genetic diseases that may have an impact on the patient now or in the future.

**H. Closure to the medical history.** Before proceeding with the physical examination, the clinician and the patient need some closure to the history. The clinician can ask if there is anything else the patient would like to discuss. The patient should be given another opportunity to add or correct historical information prior to the next step in the acquisition of data-the physical examination.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the one lettered answer or completion that is best in each case.

1. A 49-year-old, previously healthy but overweight, male, bank executive comes in with the CC: "I have a cough." He admits to smoking two packs of cigarettes a day. The man claims to be happily married and lives in Simsbury with his wife and two children. He is not taking any medication. Which of the following best illustrates the identifying data?

- (A) A 49-year-old bank executive who smokes two packs of cigarettes a day presents with the CC: "I have a cough"
- (B) A 49-year-old black bank executive presents with the CC: "I have a cough"
- (C) A 49-year-old previously healthy bank executive presents with the CC: "I have a cough"
- (D) A 49-year-old smoker from Simsbury presents with the CC: "I have a cough"
- (E) A 49-year-old happily married man with two children presents with the CC: "I have a cough"

2. A 70-year-old retired baker has a broken leg, hypertension, heartburn, IDDM, myopia, decreased hearing, and COPD. The HPI should include how many of these problems?

- (A) 3 (B) 4 (C) 5 (D) 6 (E) 7

3. A 54-year-old electrician comes in with the CC: "I have carpal tunnel syndrome." The best response is to find out

- (A) when the carpal tunnel syndrome began
- (B) the chronology of the carpal tunnel syndrome
- (C) what symptoms the patient has
- (D) how the carpal tunnel syndrome has affected the ADLs

(E) if this is the first episode

4. All of the following are components of the HPI EXCEPT

- (A) recurrences
- (B) changeover time
- (C) effects on the ADLs
- (D) etiology of symptom
- (E) location

5. Vague words that should be clarified by the clinician while taking the medical history include all of the following EXCEPT

- (A) tired ( B ) dizzy
- (C) hiccups (D) sick
- ( E ) socially

6. While taking a PMH, the clinician learns that a patient is taking digoxin, a cardiac medication. The clinician should

- (A) list the digoxin in the PMH
- (B) find out about the cardiac symptom and put it in the PMH
- (C) find out how long the patient has been taking the digoxin
- (D) find out about the cardiac symptom and put it in the ROS
- (E) find out about the cardiac symptom and put it in the HPI

7. In a PP, the category that best differentiates patients with cancer is

- (A) primary site of cancer
- (B) place of employment
- (C) number of children
- (D) response to disease
- (E) type of treatment

8. For an 85-year-old woman, all of the following components of the PMH are crucial EXCEPT

- (A) allergies
- (B) childhood history
- (C) medication
- (D) surgical history
- (E) alcohol use history

9. All of the positive findings listed below belong in the ROS of a 65-year-old man EXCEPT

- (A) occasional chest pains
- (B) occasional headaches
- (C) occasional knee stiffness
- (D) hay fever
- (E) decreased hearing

### Questions 11-15

Each description of pain that follows, select the **part** of the HPI in which it belongs.

(A) Chronology

(B) Quantity

(C) Aggravating factors

(D) Setting

(E) Quality

11. The pain starts when doing aerobics

12. The pain lasts for 10 minutes

13. The pain is like a dull, achy pressure

14. The pain occurs nightly, two or three times a week for the past 3 weeks

15. The pain increases if the patient does not stop aerobics

### ANSWERS AND EXPLANATIONS

**1. The answer is A.** Identifying data should be short, succinct sentences with a name, age, sex, occupation, and occasionally any pertinent medical information that will help in hearing or reading the HPI. In the case presented in the question, the smoking history is related to the CC of cough. Ethnicity is not an issue with this CC and should not be included. Although marital and living status are appropriate to the PP, they are not essential to the identifying data.

**2. The answer is B.** Fractured leg, hypertension, IDDM, and COPD are all active problems. Although it is safe to assume that the fractured leg is the acute problem, the three chronic problems need monitoring and treatment. The myopia, decreased hearing, and heartburn are important to note in the ROS, but unless there is some acute pain or exacerbation, they do not need the seven parameters to be explored.

**3. The answer is C.** The clinician should not accept tertiary information. Before obtaining the seven parameters of a symptom, the clinician must clarify and verify that the syndrome or disease stated in the CC is true. Without this knowledge, the clinician may miss a diagnosis and prescribe incorrect treatment.

**4. The answer is D.** The etiology of a symptom is not information that is sought from patients for inclusion in the HPI. The etiology is hypothesis-verified by the history, physical examination, and laboratory results. The seven parameters of each symptom reported by the patient, including recurrences, changes over time, effects of the ADLs, and location, are necessary to complete the HPI.

**5. The answer is C.** Vague words often have different meanings for different people. These words must be clarified so that the clinician and patient know exactly what is meant. Hiccups is the only nonambiguous word listed and does not need clarification.

**6. The answer E.** Any problem or symptom for which patients are currently being treated should be included in the HPI and have the seven parameters determined. Digoxin is a cardiac medication that cannot be forgotten and put in the PMH. Any cardiac symptom needs to be uncovered and reported in the HPI.

**7. The answer is D.** A patient's response to illness is so varied that this information helps to personalize two people with the same diagnosis. The primary site of cancer and its treatment are important medical facts that are not relevant to the PP. The number of children and place of employment are part of the PP, but without more information, these facts do not give great insight.

**8. The answer is B.** Although childhood illnesses are part of the PMH, they are less relevant for an 85-year-old woman. Rarely can 85-year-old individuals remember when and what they had as a child. If a major disease has continued through adulthood, then this will be ascertained during the adult PMH. The patient's surgical history as well as medications, alcohol, and allergies are essential in treating the patient now.

**9. The answer is A.** Occasional headache, knee stiffness, hay fever, and decreased hearing are fairly common maladies that occur in a 65-year-old man. Occasional chest pain, which may signal a cardiac problem, needs more clarification, including exploration by the seven parameters. Unless the clinician believes that the chest pain is totally benign, it should be discussed in the HPI.

**11-15. The answers are: 11-D, 12-A, 13-E, 14-A, 15-C.** The setting is the background in which a problem occurs. In this case, the pain begins while the patient does aerobics, which gives the clinician valuable information.

The length of time a symptom lasts is part of the chronology of a symptom. The chronology also includes previous episodes, duration, and any change in pattern. A pain that occurs nightly, two or three times a week for the past 3 weeks describes the chronology of the symptom.

The quality of a symptom is a description of the characteristics of the symptom. Descriptive words, such as dull, achy pressure, help to differentiate the pain. The quantity of a symptom rates the magnitude of the pain.

Aggravating factors are conditions that cause the symptom to continue to get worse. In this case, the aerobics (exercise), which increases the pain, is an aggravating factor.

## **The Physical Examination**

**I. INTRODUCTION.** The physical examination is performed in a number of clinical situations, including the office, emergency room, and hospital settings. The purpose of the physical examination is also varied. It may be performed in response to specific symptoms or to detect asymptomatic disease. This variety necessitates modification of technique. Section II of this chapter is concerned with the choreography of the physical examination, which is applicable to all physical examinations. Section III concerns the regional approach to the comprehensive

examination, which is a thorough examination performed for patients admitted to a hospital or for patients visiting a clinician for the first time. Section IV concerns the periodic health examination, which is a modification of a comprehensive physical with special emphasis on health maintenance, disease prevention, and identification of asymptomatic disease. Section V concerns directed examinations, which are further modifications of the complete examination, occurring in outpatient and emergency room settings where a more focused, time-limited examination is required.

## CHOREOGRAPHY OF THE PHYSICAL EXAMINATION.

The physical examination is conducted in a logical, flowing manner.

### A. Approach to the patient

**1. Introduction.** The examiner should provide the patient with his or her **name** and **title** (e.g., clinician, resident, or medical student) and begin the examination by **shaking hands**. Shaking hands is a socially acceptable way to initiate patient contact and is followed logically by examination of the hands and skin.

**2. Hand washing.** The examiner's hands should be washed **before every examination**, preferably in view of the patient.

**3. Explanation.** Each component of the examination should be explained to prepare the patient for anticipated maneuvers and discomfort.

**L. Position of the examiner.** Traditionally, the clinician is **on the right side of the patient** during the examination. While this is more conventional than truly essential, remaining in one position allows a more efficient examination and consistency of technique from patient to patient. Examining from the right is easier for right-handed individuals; left-handed examiners may find that **some** components of the physical are better performed from the left. In all cases, the examiner

should be comfortably stationed in relation to the patient.

### L Position of the patient

**I. Ambulatory patients on examining tables.** Patients should be seated comfortably at the end of the examining table with their legs hanging freely. As the examination progresses, patients are aided into the supine position with the footrest pulled out to support the legs. Certain examinations require that the backrest be adjusted from supine to various heights.

**! Patients in hospital beds.** The bed should be adjusted to the appropriate height for the examiner to perform each maneuver comfortably. The degree of illness or medical devices (e.g.,

intravenous lines or respirators) may necessitate alterations in the usual examination **procedure**. Special attention to patient comfort is essential.

### D. Flow of the examination

### 1. Ambulatory patients

**a. With the patient seated**, the hands and the exposed **skin** on the forearms are examined initially. The **vital signs** are then taken. A **systematic regional approach** is then followed. The **head, eyes, ears, nose, mouth, throat, neck, thorax, lungs**, and the **axillae** are examined in order. In female patients, the first portion of the **breast examination** is performed at this time.

**b. With the patient in the supine position**, the **breast examination** is completed on female patients. The **cardiovascular examination** begins in the supine position and may necessitate additional maneuvering (e.g., raising the backrest to 30°-45° or left lateral decubitus). The examination then proceeds down the body to include the **abdomen**, the **inguinal area**, the **extremities**, and the **musculoskeletal examination**. The **neurologic examination** is then initiated.

**c. With the patient standing**, the back and its range of motion, gait, cerebellar function (Romberg), and the male genitalia are examined.

**d. The rectal examination** in men and the **pelvic examination** in women are best performed as the final components of the examination.

**2. Hospitalized patients.** Patients in hospital beds or stretchers may necessitate alterations in the maneuvers or sequence used in the examination, usually due to the severity of their illness. For further detail, refer to Chapter 7 III.

## III. REGIONAL APPROACH TO THE COMPREHENSIVE EXAMINATION

**A. General appearance.** The first observations made in the physical examination are those of the patient's overall condition. These should include objective descriptions of specific information, including the following:

**1. Demographic data**, including the patient's **age, sex, and race** are noted. If the patient appears significantly younger or older than the stated age, this should be recorded.

**2. Level of consciousness** may be described as **alert, somnolent, stuporous, or comatose**.

**3. Level of distress** is an important component. Descriptive terms such as "resting comfortably," "in no apparent pain," or "in acute distress" are used to reflect this.

**4. Patient affect** should be noted. Acceptable terms are "flat," "appropriate," or "anxious."

**5. Other readily apparent observations** about the patient's physical condition are often included at this time, even if they are organ-specific. Examples include: a. "The patient is in marked respiratory distress." b. "The patient walked in without assistance." c. "The patient was brought in via stretcher and is unable to sit or stand."

**a. Rhythm** of the heartbeat is recorded as **regular** or **irregular**.

**b. Normal pulse rate** for an adult is between 60 and 100 beats a minute.

(1) **Tachycardia** is a pulse rate greater than 100.

(2) **Bradycardia** is a rate below 60.

**5. Respiratory rate.** The patient's breaths are counted for a full minute. The examiner should make these observations as discreetly as possible, since self-consciousness may lead the patient to hyperventilate.

**a. Rhythm of the respiratory pattern** is noted. Common abnormalities include:

(1) **Cheyne-Stokes respiration** (a regularly irregular sine wave-like pattern of respirations)

(2) **Biot's respiration** (an irregularly irregular pattern)

(3) **Apnea** (a prolonged period without respiratory efforts)

**b. Normal respiratory rate** for adults is *12-16* breaths a minute. **Tachypnea** refers to a rate in excess of normal, and **bradypnea** to rates below normal.

**6. Blood pressure** is accurately determined using a **sphygmomanometer** (blood pressure cuff) and a **stethoscope**. The cuff is wrapped firmly around the upper arm, 1 cm above the antecubital fossa. The stethoscope is placed over the brachial artery. The cuff is inflated until the radial pulse, as determined by palpation, is lost. The cuff is gradually deflated, while auscultating with the stethoscope. The initial sound appreciated is **systole**, and the pressure at which all sounds cease is **diastole**.

**a. Normal blood pressure** is from *100-140* systolic and from *60-90* diastolic for adults. Blood pressure greater than *140/90* is considered in the **hypertensive range**.

**b. Cuff size** should be appropriate for the patient's arm. The cuff must be large enough for the cuff bladder to encircle two-thirds of the arm. A cuff that is too small yields a falsely elevated blood pressure, and conversely, a cuff too large records a falsely low blood pressure. Blood pressure determinations are usually done in both arms with the patient sitting comfortably.

**c. Measuring orthostatics.** Many clinical situations, such as gastrointestinal bleeding or a history of syncope, require that the examiner measure the blood pressure in the supine and standing positions. These are called postural or orthostatic blood pressure readings and should be accompanied by a pulse rate determination in each position.

**d. Pulsus paradoxus.** Normal systolic blood pressure falls 3-5 mm Hg with inspiration. An exaggeration in this physiologic response is referred to as pulsus paradoxus, occurring in many disease states (e.g., cardiac tamponade, asthma, obstructive pulmonary disease, constrictive pericarditis).

(1) The examiner should determine carefully the highest pressure (systole) where sounds are audible only in expiration.

(2) The column of mercury is slowly lowered to a point where sounds are audible in both inspiration and expiration.

(3) The gap between the two measurements is the pulsus paradoxus. A gap of 10 mm or greater is considered pathologic.

**C. Skin examination** begins with the hands and forearms. The rest of the integument is exposed at the time that each section of the body is examined (e.g., skin of the back is viewed along with the chest and lung examination).

**1. By inspection** the examiner assesses:

**a. Color and pigmentation**

**b. Hair distribution**

**c. Lesions.** Each lesion is described by its **color, size, shape, distribution, and epidermal integrity.**

**2. By palpation** the examiner determines:

**a. Surface moisture** (from dry to diaphoretic)

**b. Temperature**

**c. Texture**

**d. Turgor** or resiliency, which is determined by gently pinching the skin between thumb and forefinger

**e. Elasticity**, which may be assessed concurrently

**f. Lesions**, which are palpated for firmness and assessed to be raised or flat

**D. Hands and nails**

**1. Dorsal and palmer surfaces of each hand** should be observed with attention to **color, muscular integrity, joint deformities, and skin lesions.**

**2. Finger nails** are observed for **color and deformities. Vascular integrity** is assessed by gently compressing the nail and releasing, then noting the rapidity of capillary filling.

**E. Head**

**1. Inspection**

**a. Shape and contour** of the head are assessed with attention to **symmetry** and **bony deformities.**

**b. The scalp** is examined for skin lesions.

**c. Hair distribution** is noted with reference to areas of hair loss (alopecia).

**d. The skin over each mastoid process** is inspected for ecchymoses (**Battle's sign**).

**2. Palpation**

**a. The scalp** is palpated to assess for tenderness and masses, and if there is suspected trauma, to detect depressed fractures.

**b. The examiner** may gently tug on a few hairs to determine ease of hair removal.

**F. Eyes**

**1. Conjunctiva and sclerae**

**a. The lower conjunctiva** is inspected by gently retracting the lower eyelid and having the patient look upward.

**b. The upper conjunctiva** is visible only by retracting the upper eyelid, usually employing a

sterile swab-handle as a fulcrum placed on the outer portion of the lid.

**c. Sclerae.** The **color and vascular pattern** are noted. **Hemorrhages, pigmented lesions, and**

**exudates** are noted, if present.

**2. Pupils**

**a. Pupillary size** in room light is recorded in millimeters.

**b. Pupillary light reflexes** are assessed as follows: The examiner holds a penlight at the right temple and shines it tangentially on the right eye, assuring that the light does not illuminate the left eye (Figure 6-1). The pupil being illuminated should

constrict directly to the light, while the contralateral pupil constricts consensually. This is then repeated on the left side.

**c. Accommodation.** The patient is asked to focus on an object in the distance, then to refocus on another object closer (e.g., the wall and then the examiner's finger). The pupils should constrict and the eyes converge.

**3. Extraocular movements** are tested by observing eye orientation at rest and the degree of movement of each eye.

a. The patient is asked to follow the examiner's finger as it is moved in **eight cardinal directions** in front of the patient (Figure 6-2). The patient's head should remain stationary.

**b. Nystagmus**, or involuntary rapid movements of the eyeball, in any direction should be recorded.

**c. Conjugate eye movement** is coordinated by six muscles controlled by three cranial nerves. The examiner observes for dysconjugate or nonparallel eye movement and determines which muscle and nerve are affected.

(1) CN VI supplies the lateral rectus muscles, moving each eye outward in a horizontal plane.

(2) CN IV enervates the superior oblique muscles, which control medial, downward movement for each eye.

**3. Hearing acuity** is grossly assessed by responses to whispered words spoken one foot from the patient's ear. Acuity to high-pitched sounds can be roughly tested with a watch tic or by rubbing the patient's hair between the examiner's fingers. Formal audiology testing is required for precise recording of hearing acuity.

**a. Weber test.** A 128 Hz tuning fork is placed in the center of the forehead. The vibratory sensation should be perceived in the midline or diffusely. The sound lateralizes toward an ear with a **conductive abnormality** (e.g., otitis media) and away from an ear with a **sensory-neural deficit**.

**b. Rinne test.** The tuning fork is struck and placed on the right mastoid process (measuring bone conduction), then directly in front of the right ear. The **"air" conduction** should be louder than **bone conduction**. This is repeated for the left ear.

**H. Nose.** A **nasal speculum** is introduced into each nostril with observation made regarding the mucosa, airway patency, and discharge.

**1. The nasal septum** is viewed with attention to mucosal integrity, septal deviation, and perforations.

**2. The turbinates** are viewed specifically for polyps, vascular lesions, or masses.

## **1. Mouth**

### **1. Inspection**

a. The patient is asked to open his or her mouth. A tongue blade is used to systematically expose the **gingiva**, **buccal mucosa**, and the **inferior aspects of the tongue**. Observations are made regarding **color**, **pigmentary changes**, and **mucosal lesions** of each structure.

b. The general repair and absence of **teeth** should be recorded.

**c. Normal structures, including Stensen's ducts, Wharton's ducts, anterior and posterior tonsillar pillars, and the tonsils** are identified.

**d.** When the patient is asked to protrude the tongue and say "aaah," the **uvula** should rise and fall in a midline position.

**2. Palpation.** The examiner introduces a gloved hand to palpate the tongue, area beneath the tongue, and buccal mucosa with attention to masses and tenderness.

## **J. Neck**

**1. Inspection.** The examiner inspects the neck for **symmetry**, visible **masses**, and for the **normal lordotic curvature** of the cervical spine.

**2. Range of motion** is tested by asking the patient to move the head as far as possible to the left, right, backward, and forward. The chin should reach the chest on full forward flexion.

## **3. Palpation**

**a. Lymph nodes.** Palpation of submental, submandibular, preauricular, posterior auricular, occipital, anterior cervical, posterior cervical, supraclavicular, and infraclavicular lymph nodes is done (Figure 6-3). Palpable nodes are categorized by **size, shape, consistency (i.e., soft, firm, or hard), mobility, and tenderness.**

**b. The carotid artery pulse** is palpated along the medial edge of the sternocleidomastoid muscle. The strength of all arterial pulses are recorded using a "plus" system: 2+/2 = **normal** 1+/2 = diminished pulse; 0+/2 = no palpable pulse (Table 6-1A).

## **4. Auscultation**

**a. The carotid artery** is auscultated using the diaphragm of the stethoscope, and the presence or absence of a **bruit** is recorded.

**b. Thyroid gland.** The examiner auscultates with the stethoscope over the thyroid gland, listening for a **vascular "hum."**

## **5. Thyroid gland**

**a. Inspection.** The gland may be visible in thin patients or if enlarged.

**b. Palpation.** The preferred method of palpating the thyroid gland is to have the examiner stand to the side or behind the patient and reach both hands around the neck with fingers forward. The patient is asked to swallow while the examiner feels the gland slide up beneath his or her fingers. A sip of water helps the patient swallow. Parameters recordable are the **size, symmetry, consistency,** and the presence of **nodules** or **masses.**

## **L Musculoskeletal examination**

**1.** The musculature of the upper and lower extremities is inspected with reference to size, contour, and symmetry. Muscle strength is conventionally tested as part of the neurologic examination (see III T).

**2.** All joints are inspected for deformities, edema, erythema, or warmth.

**3.** Passive **range of motion** is tested by the examiner actively moving each joint in all possible directions with only the patient's "passive" cooperation. The extent of movement is recorded. Restriction is recorded by degrees of movement (e.g., knee flexion restricted to 120°).

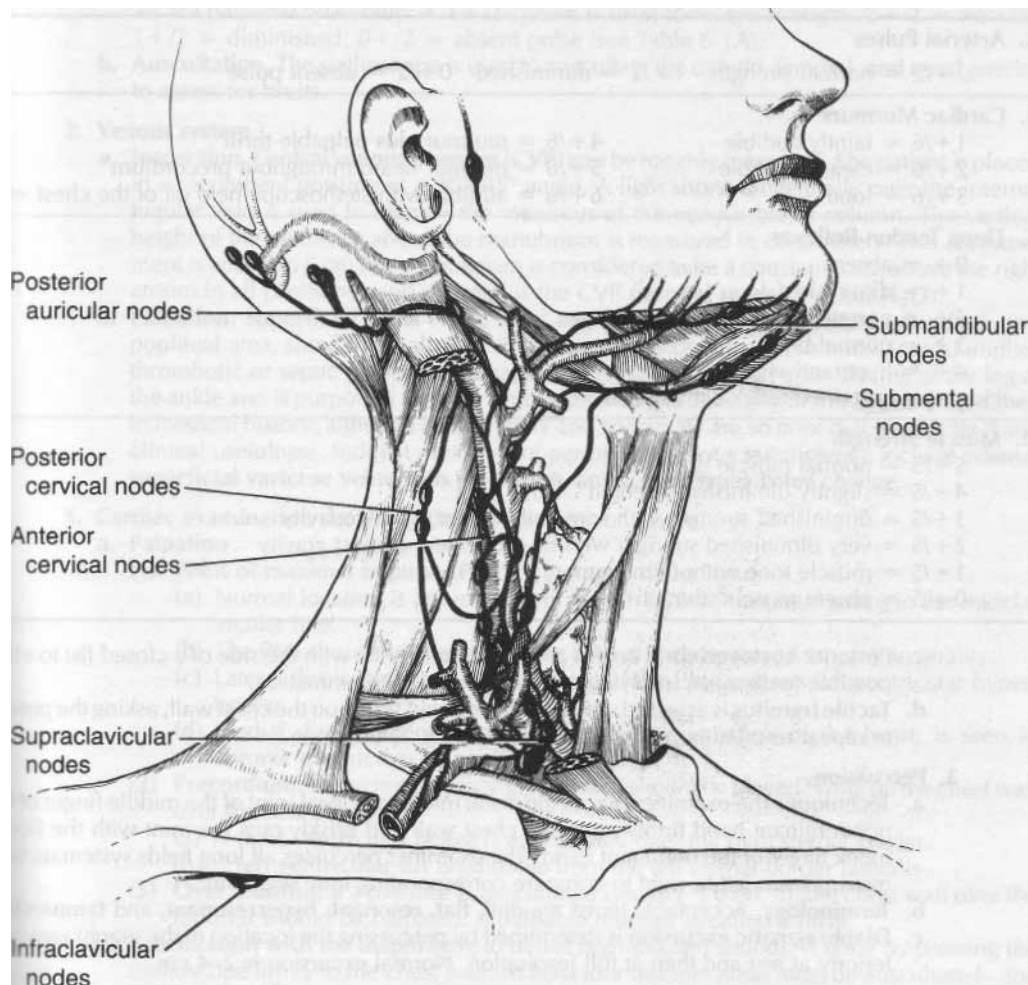
## Back examination

**Inspection: a.** The entire back is **inspected for contour.**

(1) Normal cervical and lumbar lordosis is noted 2) Abnormal thoracic kyphosis and scoliosis are described by degree of deformity.

b. Back range-of-motion is assessed with the patient standing. Flexion, extension, hyperextension, and lateral and rotary (twist) mobility are passively tested.

**Palpation: a.** The **sacral area** is palpated for edema, especially in bedridden patients. **b.** The **entire spine** is percussed to test for tenderness.



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recorde**Des**.

**Figure 1.** Lymph nodes of the head and neck.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. The patient should be in a seated position for which of the following components of the examination?  
(A) Auscultation of the heart with the bell of the stethoscope  
(B) Examination of the male genitalia  
(C) Inspection of the female breast  
(D) Palpation of the abdomen  
( E ) Percussion of the abdomen
2. A patient is brought to the emergency room in January after being found comatose in a snow bank. An electronic thermometer records a rectal temperature of 94° F. Which of the following statements about this patient's temperature is true?  
(A) An oral thermometer would measure core body temperature more accurately  
( B ) A mercury thermometer would be less accurate than an electronic thermometer  
(C) The temperature should be confirmed with an oral temperature reading  
(D) The true temperature may actually be above 94° F  
( E ) A special probe should be used in cases of potential hypothermia
3. A 75-year-old man presents for a complete physical examination. Detailed inspection of the skin includes a description of all of the following EXCEPT  
(A) skin color  
(B) hair distribution  
(C) skin turgor  
(D) skin lesions  
( E ) abnormal pigmentation
4. All of the following statements are true regarding the thyroid examination EXCEPT  
(A) a gland that is palpable is abnormal  
(B) the preferred position is for the examiner to reach both hands around the neck with the fingers forward  
(C) upon swallowing, the gland should slide upward  
(D) a vascular hum heard with the stethoscope implies hyperactivity of the gland  
( E ) a normal gland may be visible by inspection
5. An 18-year-old patient with a long history of asthma presents to an emergency room in marked respiratory distress. All of the following physical findings are likely to be

present EXCEPT  
with inspiration

(A) the diaphragm moves upward

(B) the respiratory rate is 16

(C) the patient uses the trapezius muscles on in respiration

(D) intercostal muscle retractions are noted

(E) the patient is cyanotic

6. A patient presents with a history of an irregular heart beat. All of the following procedures are correct EXCEPT

(A) the radial pulse should be palpated for 30 seconds

(B) the stethoscope should be used to auscultate on the apex of the heart

(C) the radial pulse rate should be contrasted to the apical heart rate

(D) the carotid pulse can be palpated and used to replace the radial pulse

(E) a complete cardiac examination should be performed

7. All of the following findings support venous disease in the lower extremities EXCEPT

(A) pale cool extremities bilaterally

( B ) a deep purple color

(C) bilateral edema to the knees

(D) bilateral tibia) ulcers

( E ) a palpable cord in the right popliteal fossa

8. In what order should the abdominal examination sequence proceed?

(A) Inspection, auscultation, palpation, percussion (B) Inspection, palpation, auscultation, percussion (C) Inspection, palpation, percussion, auscultation (D) Inspection, percussion, auscultation, palpation (E) Palpation, auscultation, inspection, percussion.

9. The effectiveness of the spleen examination is improved by all of the following factors EXCEPT

(A) a thin patient

(B) asking the patient to take slow deep breaths

(C) advancing the examiners fingers on expiration

(D) asking the patient to roll on the left lateral decubitus

( E ) asking the patient to place his or her left hand under the left buttocks

10. Tests of cerebellar function include all the following EXCEPT

(A) rapid alternating movements

( B ) finger-to-nose

(C) heel-to-chin

(D) Romberg reflex

( E ) deep tendon reflexes

11. A 30-year-old asymptomatic woman presents for a routine physical examination. A comprehensive periodic health evaluation for this patient should

include all of the following EXCEPT

- (A) a blood pressure recording (B) a complete breast examination (C) a pelvic examination and Pap smear  
(D) a flexible sigmoidoscopy (E) counseling on smoking and alcohol use

## ANSWERS AND EXPLANATIONS

**1. The answer is C.** The breast examination begins in the seated position to inspect for symmetry and retractions. The bell of the stethoscope is used to listen for an  $S_3$ ,  $S_4$ , and a mitral stenosis murmur. All of these are best done in the supine or left lateral decubitus position. The male genital examination should be done in the standing position to detect hernias. The entire abdominal examination is done in the supine position to decrease muscle tone and maximize access to the abdominal contents.

**2. The answer is E.** Electronic or mercury thermometers are equally effective in measuring temperature, but the preferred method of measuring core body temperature is a rectal thermometer. The limitation of an electronic thermometer is that it does not record temperatures below  $94^{\circ}$  F. Therefore, a special probe must be used in cases of suspected hypothermia as the true temperature of the patient described in the question may be below  $94^{\circ}$  F.

**3. The answer is C.** Skin turgor is determined by palpation. Turgor is determined by gently compressing the skin between the thumb and forefinger and releasing. Skin color, hair distribution, abnormal pigmentation and the presence or absence of skin lesions are all determined by inspection.

**4. The answer is A.** A normal gland may be visible and sometimes palpable, especially in thin patients. The preferred position for examination is with the examiner in the back or on the side of the patient. Normal glands should slide upward upon swallowing. In hyperthyroidism, a vascular hum can be heard, implying increased vascular blood flow.

**5. The answer is B.** A young patient in respiratory distress should have a respiratory rate far higher than 16. All other physical symptoms described are consistent with someone in respiratory distress. Trapezius and intercostal muscles are recruited to aid respiration when the patient has a respiratory compromise. Cyanosis is a physical sign, indicating lack of oxygenation.

**6. The answer is A.** Patients with an irregularly irregular heart beat require a thorough cardiovascular evaluation, including a complete cardiac examination. Either the radial pulse or the carotid pulse can be palpated for a minimum of 60 seconds. This should be contrasted to the apical heart rate as heard by auscultation with the stethoscope, since some arrhythmias present with a pulse deficit as recorded peripherally.

**7. The answer is A.** Pale cool extremities suggest arterial insufficiency. Venous insufficiency presents with edema, a violaceous hue, and in severe cases, with skin ulceration. A deep venous thrombosis is suggested by a palpable cord in the popliteal area.

**8. The answer is A.** A careful detailed inspection should be the first component of every examination. The examination sequence for the abdominal examination differs from that of the chest or cardiac examination. Auscultation must come before palpation and percussion. Palpation and percussion may alter bowel sounds (i.e., decrease or increase their intensity). Auscultating first gives a more accurate representation of true bowel sounds.

**9. The answer is D.** Even normal spleens may be palpable in a thin patient. The technique of the examination is to have the patient take slow deep breaths and advancing fingers on expiration. The spleen becomes easier to palpate if the patient rolls to the right lateral decubitus position or places his or her left hand under the left buttock.

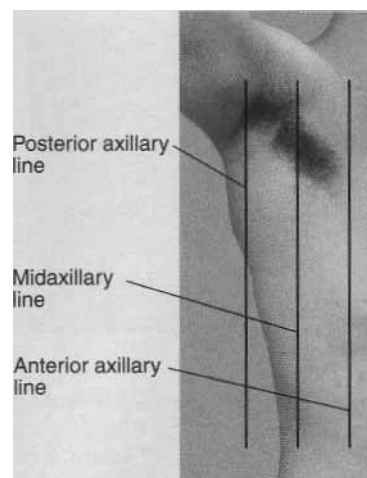
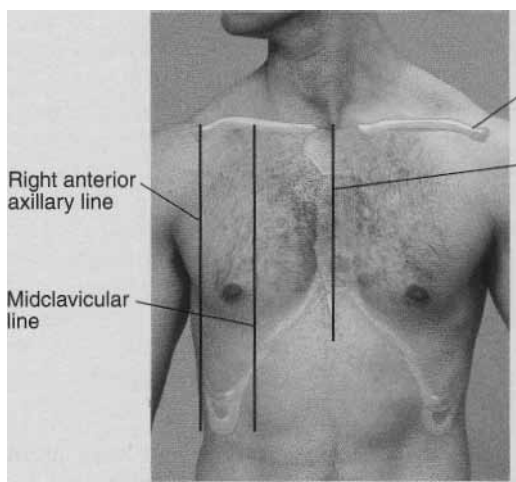
**10. The answer is E.** Careful examination of cerebellar function includes testing arms, legs, and gait. Rapid alternating movements and finger-to-nose both test upper extremity coordination. Heel-to-toe measures lower extremity cerebellar function. Romberg reflex and gait test overall cerebellar function. Deep tendon reflexes do not test cerebellar functions.

**11. The answer is D.** The purpose of a comprehensive periodic health examination is to detect asymptomatic diseases for which the patient is at high risk as well as providing an opportunity for health risk identification and counseling. Blood pressure recording is recommended for all age-groups. A menstruating female should have a yearly breast examination and a biannual pelvic examination and Pap smear. Counseling on health risk, such as smoking and alcohol use, are crucial. While the recommendation for flexible sigmoidoscopy is controversial, the asymptomatic patients should not begin routine sigmoidoscopies until age 40 or 50.

## The Thorax and the Respiratory Tract Examination

### General Information

1. Methodical inspection of the thorax requires reference to established "landmarks" to locate specific structures and to report significant findings.
2. The same structural landmarks are used in examining both the lung and the heart.
3. It is important to visualize the underlying structures and organs when examining the thorax.



### INSPECTION

#### 1. Inspection

- a. **The chest wall** is inspected for **symmetry** and **contour**.
- b. **The anterior-to-posterior (AP) diameter** is compared to the lateral dimension (AP should be less than lateral).
- c. **The thoracic spine** is inspected for scoliosis and exaggerated kyphosis.
- d. **The respiratory effort** is inspected, including:
  - (1) Overall **ease** or **difficulty** of respiration
  - (2) **Paradoxical diaphragmatic movement** (normal: diaphragm down with inspiration; abnormal: diaphragm up with inspiration)
  - (3) **Use of accessory muscles**, such as trapezius, strap muscles, or sternocleidomastoids
  - (4) **Intercostal muscle retractions** (abnormal)

Inspect the anterior, posterior, and lateral sides of the thoracic cage. During this initial step, note the presence of any **chest wall deformities**, such as barrel chest, pectum excavatum (tunnel chest) and pectum carinatum (pigeon chest). Note

any operative scars. Observe the spine and note any deformities, such as kyphosis and scoliosis. Observe the breathing movements, and note any irregularities in frequency and rate; observe the equal motion of the chest. Pay special attention to patterns of breathing, such as Kussmaul, Cheyne-Stokes, and Biot breathing (Table 2 at the end of this part). Also observe the use of accessory muscles during the inspiratory effort. Note the patient's conversation during the clinical exam, paying special attention if the patient tolerates the lying down position. Do not forget the two classic types of chronic obstructive pulmonary disease (COPD) patients. The **pink puffers** are characteristic because no cyanosis is noted, they are relatively elderly (i.e., older than 60 years), thin, usually do not present cough or expectoration. Further studies in these patients reveal that they have a predominant emphysema component, hypocapnia, and mild increase in airway resistance. The **blue bloaters** have the tendency to be cyanotic from hypoxia and bloated from right side heart failure (HF). They predominantly have a chronic bronchitic pattern more common in young age individuals, and they experience chronic cough, expectoration, and rhonchi. Finally, continue with the clinical exam of the patient in supine position, noting the cardiac area. Note the heart's apical impulses, which are easier to observe in thin individuals (see down).

## PALPATION

- a. **Chest wall exertion** is tested by placing the examiner's hands on the lower posterior chest wall bilaterally and asking the patient to take a deep breath. Symmetry of **movement** is noted.
- b. **Spine.** The examiner lightly **raps the vertebral processes** from the cervical to sacral spine to assess tenderness.
- c. Posterior **costovertebral angles** are **percussed** lightly with the side of a closed fist to elicit possible tenderness, implying renal or perirenal inflammation.
- d. **Tactile fremitus** is assessed with both hands held firmly on the chest wall, asking the patient to repeat resonating phrases, such as "99" or "blue moon."

Start by palpating gently over the bones and on the cartilages. Pay special attention to any local tenderness. Note the presence of air in the subcutaneous tissues (surgical emphysema). Palpate thoroughly, and always ask the SP to guide you where he feels the complaint. Perform the following maneuvers (**Vocal fremitus**): place your palms on the thorax surface and then ask the patient to say different words or numbers, such as 13, 98, and so forth. Remember that the passage of air in the normal lung is due to a specific consistency of the lung tissue and thus normal vibration sounds are transmitted to the chest surface. Any alteration on this normal characteristic, such as a mass consolidation, lobar pneumonia, or

fluid-filled pleural space, will alter the transmission of sound in the vocal fremitus. For practice, first start recognizing the normal sensation on the normal lung; then you will notice the difference when you see an abnormal case. In general, the sound will be **increased** in consolidation (e.g., tumors, lobar pneumonia), **decreased** if there is air (pneumothorax), air/fluid levels (pleural effusion) or pleural thickening between the lung and the chest wall. **Vocal resonances** the same test as vocal fremitus, but it is performed by placing the stethoscope on the thorax. (For more information, see auscultation section). **Chest expansion** is examined by placing both hands on the anterior thorax and the posterior surfaces of the thoracic cage and noting the chest movements. The thorax movements need to be symmetric in both hemithorax. (**Respiratory excursion**), is assessed by placing the palms of your hands and thumbs symmetrically in both hemithorax at the same time, on the level of the eleventh ribs on the posterior area, and then on the anterior surface to the sides along each costal margin. Then ask the SP to breathe deeply. Observe the movement of your hands over the skin on the thoracic cage: normal movements are symmetric during the chest expansion (inspiration) and during the passive reduction or expiration movements. Pay special attention to any abnormality in the respiratory movements. Alterations can be less movement in one side due to pleural effusion, lung collapse, pneumothorax, and pneumonia. A bilateral stopping movement due to pain is seen in pleuritis. Decreased movements in both sides are seen in generalized lung fibrosis and in chest wall problems, such as ankylosing spondylitis.

### 3. Percussion

**a. Technique.** The examiner places the distal interphalangeal joint of the middle finger of the nondominant hand firmly upon the chest wall and briskly raps the joint with the flexed index finger of the dominant hand. The examiner percusses all lung fields systematically, moving from left to right to compare corresponding lung segments.

**b. Terminology.** Acceptable terms are **dull, flat, resonant, hyperresonant, and tympanitic**.

**c. Diaphragmatic excursion** is determined by percussion the location of the diaphragm posteriorly at rest and then at full inspiration. Normal excursion is 2-4 cm.

The main purpose is to detect the **resonance** (hollowness) or **dullness** of the chest. First, be familiar with the normal percussion sound of the thoracic cavity—that is, the normal resonance of the lungs, the dullness of the liver, the tympanic sound of the gastric bubble.

### 4. Auscultation

**a. Technique.** The diaphragm of the stethoscope is pressed firmly to the chest wall in the intercostal areas. All lung zones are auscultated, again moving back and forth to test for symmetry. A full examination must include auscultating anteriorly, especially at the apices **and** lower over the right middle lobe and lingula.

**b. Terminology**

(1) **Normal breath sounds** are described as **vesicular**.

(2) **Abnormal, or adventitious,** sounds include:

(a) **Crackles**, which are fine high-pitched sounds (qualitatively like hair being rub

between two fingers), usually on inspiration

(b) **Wheezes**, which are high-pitched sounds on expiration or inspiration

(c) **Rhonchi**, which are coarse, variable sounds with inspiration and expiration

**c. Vocal fremitus** is elicited by asking the patient to whisper the number "99" and assess

uniformity of sound transmission in all zones.

**d. Egophony ("E-A change")** is tested by auscultation while the patient says a prolonge

"EEEE A solid or liquid mass will alter the transmission of the sound to an "AAA".

sound.

The normal breath sounds heard over the normal lungs are two types: the **vesicular breath sounds** and the **bronchial breath sounds**. The abnormal breath sounds often are called **added sounds**, and these can be classified as **crackles, wheezes, stridor, and rubs**.

The **vesicular breath sounds** are produced in the small airways. They are transmitted through the airways and then attenuated by the lung structure through which they pass. The **bronchial breathing sound** is produced in the large airways, and is transmitted more or less unchanged through the lung tissue. The transmission of this sound is increased when the lung tissue itself acts as a **solid mass**, a good conductor for the wave sounds transmitting it from the origin site (central airway) to the skin (stethoscope bell). Those characteristics are like the vocal fremitus or vocal resonance. If a tumor is obstructing the central airway, there will not be transmission of sound, and then no bronchial breathing will be heard.

The following are descriptions of abnormal, or added, sounds:

**Crackles** are produced by air passage through the large bronchi that impacts with the secretions on it. They may be described as **fine crackles** that occur elsewhere in the lung tissue and are caused by bronchiectasis, pneumonia, pulmonary edema, and so forth. This sound is very similar to the sound produced by rolling the hair close to the ears.

**WHEEZES** are produced by the narrowing of the airway from any cause (e.g., asthma, COPD). If you suspect asthma in a patient and you believe that he or she has a severe attack (e.g., respiration > 28 bpm, heart rate > or = 110/min), you might check the presence or absence of pulsus paradoxus to confirm your diagnosis. Check the blood pressure, and see if it decreases by 10 mm Hg or more on deep inspiration. In an otherwise healthy patient, the BP changes are less than 5 mm Hg.

**Stridor** is better heard without a stethoscope and close to the patient's mouth. This sound indicates an obstruction or narrowing of the larynx, trachea, or main bronchi. For example, it is heard in epiglottitis.

**Rubs** are caused by inflammation of the pleural surfaces due to pneumonia, pulmonary embolism (PE), and so forth. They frequently are associated with pain on deep inspiration.

The reduction on vesicular breath sounds can be expected in severely obstructed airways (e.g., in asthma), emphysema, or in obstruction by a mass or tumor. The breath sounds are markedly reduced in emphysema, pneumothorax, over a particular bullae, pleural effusion, and pleural thickening. In general, any alteration between the lung and the chest wall will cause reduction in the breath sounds. It is important to mention some symptoms that are directly related to the respiratory system, such as cough.

**Cough** is a common complaint that you may encounter in a routine practice as well as on the CSA exam. This is a nonspecific symptom that may be produced by several factors that cause irritation on the tracheobronchial tree. Common causes can be infections, toxic substances, and neoplasms. Cough may be accompanied by other symptoms in lung diseases.

The differential diagnosis is wide, but depending on the medical history and physical findings, it can be narrowed. Not every examination or diagnostic workup is necessary. The overall assessment determines which tests are necessary for each patient; use your own criteria. If you have a patient/SP with systemic and cough symptoms that suggest that he has tuberculosis (TB) and you believe that he is a candidate for chemoprophylaxis, be prepared to discuss with him the possibility of it if a patient's skin test becomes positive.

## **DIAGNOSTIC PROCEDURES IN RESPIRATORY DISEASES**

The *roentgenographic examination* of the chest represents the cornerstone of the diagnostic workup of the patient with suspected pulmonary disease, and it is the integration of the information obtained from the clinical examination and the roentgenogram which often provides the key to diagnosis. Every effort must be made to obtain past chest x-rays.

Gross abnormalities of thoracic structure; pulmonary, mediastinal, and pleural masses; parenchyma consolidation; cysts; cavities; and abnormalities of the pulmonary vascular bed are all detected reliably by roentgenography.

Computed tomography, magnetic resonance imaging, thoracic ultrasound, angiocardiology, and pulmonary scintigraphy are additional imaging

modalities which may be helpful in establishing a diagnosis in a patient with an abnormality on the plain chest roentgenogram.

Thoracic **computed tomography (CT)** has essentially replaced standard tomography (laminography, planigraphy). Both techniques provide a sequence of images, each representing a "slice of the lung" at a different depth. Ordinarily, "cuts" are made at 0.5- to 1.0-cm distances through the areas of interest. These procedures can identify a number of features that are not appreciated on the "routine" roentgenogram, including calcium in a solitary nodule (which if diffuse or in concentric rings signifies a benign etiology); a cavity within a mass lesion; and the presence of hilar, paratracheal, and subcarinal node enlargement. The CT scan is particularly useful in the definition of pleural disease (e.g., differentiating fluid from tumor; identifying calcium in asbestos-exposed individuals); with contrast injections, in differentiating tissue masses from vascular structures; and in identifying small parenchymal nodules. However, to some extent, the sensitivity of CT is a mixed blessing because it is still not known how many "normal" individuals have pleural or parenchymal abnormalities by CT and how these small, benign, hitherto undetected lesions can be distinguished from neoplastic lesions. The CT scan is also proving useful in the detection of interstitial lung disease not apparent (or equivocal) on routine chest roentgenogram and in quantifying emphysematous changes.

**Magnetic resonance (MR)** imaging remains, in terms of its value in pulmonary diseases, an investigational technique. It has potential value in achieving fine definition of mediastinal lesions, pleural lesions, and, perhaps, in defining embolic occlusion of major pulmonary arteries.

**BRONCHOGRAPHY** In this method, radiopaque material is instilled into the tracheobronchial tree via a catheter or bronchoscope. In most situations in which bronchography was used in the past (e.g., for the diagnosis of bronchiectasis), it has been replaced by chest CT.

**Bronchoscopy, bronchial brushings, and bronchoscopic biopsy** have been greatly facilitated by the development of the fiberoptic bronchoscope.

**BRONCHOSCOPY** The primary objectives of bronchoscopy include direct visualization of the tracheobronchial tree, including abnormalities such as tumors or granulomatous lesions; biopsy of suggestive or obvious endobronchial lesions; and lavage, brushing, or biopsy of lung regions for cultural and cytologic examinations. Both the *diagnostic reach* of and *accessibility to* bronchoscopy have been expanded by the flexible fiberoptic bronchoscope (FOB). This can be understood best by comparing the FOB with the "standard" rigid bronchoscope.

The rigid bronchoscope is a wide-bore metal tube that incorporates a lighted mirror-lens system. The FOB is composed of fiberoptic bundles that provide both illumination and visualization pathways. One or more small channels with a diameter of 1 to 3 mm traverse the FOB, through which instruments can be passed, fluids delivered, and suction applied. The rigid bronchoscope comes in various external diameters limited only by the feasibility of introducing to FOB.

Even in the presence of massive hemoptysis, FOB with appropriate precautions can yield useful information. Patients with bronchospasm (or a history of bronchospasm) are at particular risk of acute enhancement of spasm and should be approached after good preparation and with resources for intubation-ventilation at hand. The primary contraindication to both rigid and fiberoptic bronchoscopy is the same: performance by inexperienced personnel. Lack of experience sharply reduces diagnostic and therapeutic yield while increasing risks.

A variety of **other diagnostic procedures** are helpful in the workup of the patient with known or suspected pulmonary disease. These include **skin tests for tuberculosis, histoplasmosis, and a variety of other fungal infections, scratch or intradermal tests to detect atopic reactions, appropriate serum complement fixation tests, and examination and culture of the sputum, pleural fluid, and bronchial washings.**

**SKIN TESTS** Having arrived at a tentative list of diagnostic possibilities based on the history, physical examination, and radiographic appearance, the physician should move to other procedures. One of the simplest, least costly, and most commonly overlooked is the application of *skin tests* with specific antigens. Antigens are now available to assist in the diagnosis of **tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, trichinosis, toxoplasmosis, and aspergillosis.**

**SEROLOGIC TESTS** These relatively inexpensive tests also may be useful in the diagnosis of histoplasmosis, blastomycosis, coccidioidomycosis, toxoplasmosis, *Mycoplasma pneumonia*, Legionnaires' disease, a variety of other infectious diseases involving the lungs, and certain immunologically mediated lung diseases (e.g., lupus erythematosus, Wegener's granulomatosis)..

#### **SPUTUM EXAMINATION**

It is important that the specimen contain sputum, not saliva, the latter being identified by the presence of squamous (mouth) rather than epithelial (bronchial) cells. The gross nature of the sputum-color, odor, and the presence of blood-may provide valuable clues; e.g., foul sputum suggesting anaerobic pulmonary infection, and blood, in any amount, indicating an abnormality that mandates further investigation. Carefully stained smears of the sputum should be examined next, for these may disclose the causative organism in many bacterial pneumonias, tuberculosis, *Pneumocystis pneumonia*, and in some fungus infections. Sputum eosinophilia can suggest the presence of reversible airway disease responsive to glucocorticoids; hemosiderin-laden macrophages suggest the possibility of Goodpasture's syndrome. Often valuable time is lost because the sputum smear is not examined and results of culture are awaited instead. Sputum samples can be obtained from patients who are not coughing by having them inhale a heated mixture of a mildly irritative solution that induces cough. Such induced samples have been particularly useful in the diagnosis of *P. carinii* pneumonia and in obtaining cytologic specimens for the diagnosis of

carcinoma of the lung. Careful handling of such specimens and interpretive expertise heavily determine the diagnostic yield.

*Culture* of expectorated sputum (spontaneous or induced) are invaluable for identification of organisms responsible for tuberculous and fungus infections. Blood cultures may be useful in certain contexts, particularly in AIDS patients with *Mycobacterium avium-intracellulare* (MAI) infections in whom sputum examinations are often negative.

Beyond such standard approaches to obtaining material for culture, **five procedures**, described below, are now gaining wide acceptance because they limit oropharyngeal contamination and/or can be used to obtain representative samples of lung secretions from the area of lung involvement: **(1) catheter-brush sampling, (2) bronchoalveolar lavage, (3) transtracheal aspiration, (4) transbronchial lung biopsy, and (5) percutaneous needle aspiration of the lung.**

**PULMONARY FUNCTION TESTS** Certain "patterns" of derangement in spirometric tests, arterial blood gases, diffusing capacity, and other functional parameters are particularly suggestive of certain pulmonary diseases. For example, diffuse interstitial fibrotic diseases of the lungs produce a "restrictive" spirometric defect, reduced pulmonary compliance, a reduced diffusing capacity, and an alveolar-arterial oxygen tension difference that is widened at rest and widens further with exercise. Emphysema characteristically causes expiratory obstruction, lung hyperinflation, decreased static elastic recoil (increased compliance), and a reduced diffusing capacity.

**TRANSTRACHEAL, CATHETER-BRUSH, AND PERCUTANEOUS NEEDLE ASPIRATION OF THE LUNG** All three of these procedures are used to obtain material for culture and microscopic examination. In the case of culture, all three techniques bypass the oropharyngeal flora, though transtracheal aspiration is the least certain in this regard.

**BRONCHOALVEOLAR LAVAGE** This procedure is usually performed by lightly wedging a fiberoptic bronchoscope in distal airways, gently irrigating the air spaces beyond with saline, and analyzing the cells obtained. A "liquid biopsy" of the contents of the distal air spaces is obtained. The procedure has value in the diagnosis of *P. carinii* pneumonia and other infections, in alveolar proteinosis, and in some patients with interstitial pneumonitis of uncertain cause. Maximum diagnostic yield requires careful techniques and expert sample processing.

**THORACENTESIS AND PLEURAL BIOPSY** Thoracentesis should be performed to obtain pleural fluid in all pleural effusions of uncertain etiology and may be indicated for relief of symptoms in some patients with effusion of known cause.

Pleural fluid obtained should be examined for specific gravity, white blood cell count and differential, protein and glucose concentrations, lactic acid dehydrogenase (LDH), pH, and amylase. Gram stain, cultures, and exfoliative cytologic specimens should be obtained, and, in some instances, rheumatoid factor and complement levels are measured.. A pleural fluid LDH above 200

IU, a pleural fluid/serum protein ratio greater than 0.5, and a pleural fluid/serum LDH ratio greater than 0.6 all indicate that an "exudative" rather than "transsudative" process is present. A low **pH** (<7.20) often indicates that an empyema, probably requiring tube drainage, is present. Specific diagnostic findings in pleural fluid may include the opalescent, pearly fluid characteristic of chylothorax; positive smears or cultures for tuberculosis or other infections; a marked elevation of amylase indicative of effusion secondary to pancreatitis or a ruptured esophagus; and the very low glucose values often seen in effusions associated with rheumatoid arthritis.

Pathology of the respiratory system frequently gives rise to consistently clustered groups of **clinical signs, symptoms, and laboratory findings** called *syndromes*.

*Main syndromes in pulmonology*

| <b>Syndrome</b>                            | <b>Palpation<br/>(Fremitus)</b> | <b>Percussion</b>    | <b>Auscultation</b>   | <b>DIAGNOSTIC<br/>PROCEDURES</b>  |
|--|---------------------------------|----------------------|---|---|
| <b>Consolidation</b>                       | <b>Increased</b>                | <b>Increased</b>     | <b>bronchial<br/>breath<br/>sounds, fine<br/>crackles</b>         | <i>roentgenographic<br/>examination</i> of<br>the chest<br>(parenchyma<br>consolidation)                        |
| <b>Pleural<br/>Effusion</b>                | <b>Decreased</b>                | <b>Dullness</b>      | <b>No breath<br/>sounds, no<br/>crackles</b>                      | <i>roentgenographic<br/>examination</i> of<br>the chest,<br>thoracocentesis,<br>pleural effusion<br>examination |
| <b>Atelectasia</b>                         | <b>Decreased</b>                | <b>Hyperresonant</b> | <b>No breath<br/>sounds, no<br/>crackles</b>                      | <i>roentgenographic<br/>examination</i> of<br>the chest,<br>atelectasia   |
| <b>Pneumothorax</b>                        | <b>Decreased</b>                | <b>Hyperresonant</b> | <b>No breath<br/>sounds, no<br/>crackles</b>                      | <i>roentgenographic<br/>examination</i> of<br>the chest,  |
| <b>Chronic<br/>airflow<br/>restriction</b> | <b>Decreased</b>                | <b>Hyperresonant</b> | <b>WHEEZES</b>  | <b>Spirographia,</b><br>FEV <sub>1</sub> /FVC ratio   |
| <b>Lung fibrosis</b>                       | <b>Increased</b>                | <b>Increased</b>     | <b>bronchial<br/>breath<br/>sounds,<br/>crackles,<br/>wheezes</b> | <i>roentgenographic<br/>examination</i> of<br>the chest,  |

## STUDY QUESTION

**DIRECTIONS:** Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

1. A patient with low-grade fever and weight loss has poor excursion on the right side of the chest, with decreased fremitus, flatness to percussion, and decreased breath sounds all on the right. The trachea is deviated to the left. Likely diagnosis is

- a. Pneumothorax
- b. Pleural effusion
- c. Consolidated pneumonia
- d. Atelectasia

2. A 60-year-old female with a history of urinary tract infection, steroid-dependent chronic obstructive lung disease, and asthma presents with right side infiltrates and an eosinophil count of 15%. She had all findings at right side: BESIDES:

- a) RONCHI,
- b) DECREASED FREMITUS,
- c) flatness to percussion,
- d) decreased breath sounds

3. A 40-year-old alcoholic develops cough and fever. Chest xray shows an air-fluid level in the superior segment of the right lower lobe. He had all findings at right lower lobe side: BESIDES:

- a) RONCHI,
- B) INCREASED FREMITUS,
- c) flatness to percussion,
- d) decreased breath sounds

4. A 64-year-old woman is found to have a left-sided pleural effusion on chest x-ray.

Which of the following will be discovered in this patient?

- a. increased fremitus
- b. ronchi
- c. haemoptysis
- d. flatness by percussion
- e. increased breath sounds

5. A 40-year-old man without a significant past medical history comes to the emergency room with a three-day

history of fever and shaking chills, with a 15-minute episode of rigor, nonproductive cough, and anorexia, as well as the development of right-sided pleuritic chest pain and shortness of breath over the last 12 hours. A chest roentgenogram reveals a consolidated right middle lobe infiltrate, and a CBC shows an elevated neutrophils count with many band forms present. Which of the following statements is correct?

- a) he has pleural effusion
- b) it is dullness by percussion on right side
- c) he hasn't pleural noise
- d) many neutrophils band forms present suggest absence of inflammation.

**6.** The most likely finding in a patient with acute pulmonary embolus is all, **beside**

- a. Wheezing
- b. Pleuritic chest pain
- c. Tachypnea
- d. Haemoptysis
- e. Right-sided S<sub>3</sub> heart sound

**7.** A 65-year-old male with mild congestive heart failure is to receive total hip replacement. He has no other underlying diseases, no history of hypertension, recent surgery, or bleeding disorder. The best approach to prevention of pulmonary embolus in this patient is

- a. Aspirin-75 mg per day
- b. Aspirin-325 mg per day
- c. Warfarin
- d. Early ambulation

**8** The hallmark of asthma that distinguishes it from other obstructive airway diseases is that in asthma:

- a. Hyperinflation is present on chest roentgenogram
- b. Airway obstruction is reversible
- c. Hypoxia occurs as a consequence of ventilation-perfusion mismatch
- d. The FEV<sub>1</sub>/FVC ratio is reduced

e. Exacerbation often occurs as a result of an upper respiratory tract infection

9. 45-year-old man with bronchial **asthma** complains of a **productive cough** and **hemoptysis**.

He also complains of progressively increasing breathlessness with intermittent attacks of severe dyspnea.

Which of following physical exam finding do **not belong** that patient?

- a) **tachypnea**
- b) clubbing of fingernails
- c) wheezes
- d) **eosinophilia**
- e) dullness to percussion

10. A 76-year-old male presents to the emergency room with **confusion** and a **severe cough**.

The patient's illness began with the **abrupt onset of headache, muscle aches, and weakness** followed 24 hours later by **high fevers and shaking chills**. He subsequently developed a **nonproductive cough with pleuritic chest pain, dyspnea, nausea, vomiting, and diarrhea**. He is a chronic **smoker** and drinks heavily, Vital Signs: **high fever** (40.0 C); **bradycardia (HR 50)**; tachypnea (26 /min); normal BP. Physical Examination: disoriented; diaphoretic; **crackles bilaterally**. Cell Blood Count: **elevated WBC** (18,000). Electrolytes: **hyponatremia**. Gram stain of sputum reveals numerous neutrophils and no bacteria; **increased Legionella titers**, patchy bronchopneumonia.

Which of following physical exam finding do **not belong** that patient?

- a. bradypnea
- b. fine whizzing
- c. haemoptysis
- d. flatness by percussion
- e. increased breath sounds

## Answers and explanations

**1. The answer is b. - Pleural effusion . Pneumothorax** – *Free air between the visceral and parietal pleurae*, characterized by tympani by percussion.

**Consolidated pneumonia** - characterized by increased fremitus. **Atelectasia** - *A shrunk, airless state affecting all or part of a lung*, characterized by the trachea and heart are deviated toward the affected side.

**2. The answer is b. Decreased FREMITUS.** Patient had pneumonia. Pneumonia: An acute infection of lung parenchyma including alveolar spaces and interstitial tissue. During physical examination most common symptoms include ronchi, percussion dullness, decreased breathing sounds and INCREASED fremitus..

**3. The answer is a. Wheezing . Lung abscess** characterized by INCREASED FREMITUS, dullness by percussion, decreased breath sounds and no **Wheezing** .

**4. The answer is d. dullness by percussion.** See #1.

**5. The answer is b.** it is dullness by percussion on right side. Fibrous Plevritis is characterized by absence pleural effusion, presence of pleural friction rub, inflammation with many neutrophils band forms present.

**6. The answer is a. Wheezing.** Pulmonary embolus leads to development of pulmonary infarction. **Pulmonary infarction (PI)** is hemorrhagic consolidation (often followed by necrosis) of lung parenchyma with Plevritis chest pain, . Tachypnea, Hemoptysis and no wheezing.

**7. The answer is c.** Warfarin is the principal agent recommended for the prophylaxis of acute pulmonary embolus in patient who receive total hip replacement. Warfarin is started preoperatively, the daily dose is adjusted to maintain an international normalized ratio (INR) of 2 to 3. The value of aspirin in this setting is unclear. Early ambulation and elastic stockings are also important in preventing thromboembolism, but are not adequate in themselves in this high-risk situation.

**8. The answer is b. Airway obstruction** is reversible. All others is present in all obstructive airway diseases.

**9. The answer is a. dullness by percussion.** Bronchial **asthma** characterized by emphysema and **hyperresonant** by percussion, tachypnea, clubbing of fingernails, wheezes, eosinophilia.

## The Cardiovascular System Examination

### Chief complaints

The most common symptoms of heart disease are **dyspnea, chest pain, palpitations, edema and syncope**. None of these are pathognomonic of cardiac disease and its interpretation depends on the entire clinical picture.

**Chest pain** is a common complaint and their presence announces multiple problems on different systems, such as musculoskeletal, respiratory, cardiac, and gastrointestinal systems. The most common cause of acute chest pain related to cardiac problem is ischemia. Dyspnea may be a sign of cardiac disease and indicate an elevated left atrial and pulmonary venous pressure or fluid overload.

**Dyspnea** may also be caused by pulmonary disease. Cardiac dyspnea should be quantified by the amount of activity that precipitates it

a. Other terms to describe this symptom include **orthopnea** and **nocturnal paroxysmal dyspnea**.

**Orthopnea** is a dyspnea that occurs in recumbency, and the nocturnal paroxysmal dyspnea is an acute shortness of breath (SOB) episode that awakens the patient at night, occurs 30 minutes to 2 hours after going to bed, and is relieved by sitting or standing up. Ask the patient the number of pillows -- ~ that he or she uses to relieve his or her symptoms to sleep well at night.

**Edema** is a common complaint in patients with heart failure. Do not forget to examine his or her legs. One way to document signs of cardiac edema is to measure and document the patient's weight during the physical exam if previous weight is known.

**Palpitations** are another symptom that may indicate cardiac disease. Palpitations are an awareness of the heart beating irregularly, rapidly, or unusually forcefully within the chest. Palpitations can be a normal phenomena that occur in athletes or in normal individuals; it is often associated with caffeine intake. Palpitations alone may be a symptom of diverse problems. When palpitations are due to cardiac arrhythmia, they may be accompanied with syncope and light-headedness. It is important to make an appropriate analysis of this symptom. Questions about rhythmicity, or episodic skips or thump (by ectopic beats), can give clues about the underlying problem. Ask the patient: *How do you, feel your car diac rhythm? Is it regular or irregular?* Other questions may help you distinguish between palpitations caused by sinus tachycardia from paroxysmal arrhythmia: Did the palpitations settle down gradually? Or did they stop suddenly like turning off a switch? Final distinguishing between these conditions depends on the patient's history, ECG, or continuous Holter monitoring. Remember, you need to consider a range of possible diagnoses (up to five). Table 3-14 lists a differential diagnosis of palpitations.

**Syncope** is an abrupt decrease in cerebral perfusion causing brief loss of consciousness (i.e., fainting). Fainting itself can be due to benign conditions. When syncope is the chief complaint, you must try to determine whether the

cause is benign or if there is a life-threatening condition (e.g., ventricular arrhythmia). The differential diagnosis is wide, but there are some clinical clues that may help you determine the cause of syncope (e.g., the presence of aura in seizures, history of sudden raising from bed or chair in orthostatism, sudden loss of consciousness in arrhythmias).

**Elevated blood pressure (> 140/90 mm Hg)** is another symptom that may be present by patients with complains on heart deseas.

### **History of present illness (HPI)**

### **(Anamnesis morbi)**

The HPI should include only symptoms - that is, information that the patient reports about changes in function, appearance, or sensation.

**Seven parameters of each symptom** are needed to complete the HPI (see a-g below). Often asking the patient an open-ended question, such as, "Take me from the time you noticed the back pain until today and describe what happened," will provide the clinician with most of the parameters. Details can then be obtained by asking additional questions.

**a. Chronology** of the symptom from the time it first started to the present time must be de termined. An **acute exacerbation** of a problem should be described first (using the parameters listed below). The clinician then goes back to the onset of the problem and describes the entire chronology up to the acute event.

**b. Quality.** The quality of a symptom is a detailed description of what exactly the symptom is.

**c. Quantity** of a symptom is the magnitude or intensity.

**d. Location.** It is important that the patient identify where the symptom is located.

**e. Setting** is the context in which the symptom occurs.

**f. Alleviating and aggravating factors** include any activity, event, or attempted makes the symptom better or worse;

**g. Associated symptoms** are other symptoms that occur with or during the course of illness

**h. Complications.** Predictable complications of any extant chronic disease should be although they are not considered one of the seven parameters. Some complications are serious and may need to be presented separately; for example, a patient may have; failure as a complication of diabetes mellitus.

Patient's description of symptoms. The HPI should include only symptoms-that is, information that the patient reports about changes in function, appearance, or sensation. A symptom is a subjective description. The HPI should not include signs, which are any abnormalities discovered by the clinician on direct observation or examination-that is, an objective indicator.

### **Past medical history (PMH)**

### **(Anamnesis vitae)**

The PMH is obtained to ascertain any medical information from the patient's past that may have an impact on the present or future.

a. Childhood illnesses

b. Adult illnesses.

c. Surgical procedures.

d. Accidents and injuries

e. Occupational history

f. Immunizations

g. Obstetric history.

h. Psychiatric history.

i. Medications.

i. Health habits

(1) Exercise.

(2) Diet.

(3) Alcohol

(4) Tobacco

k. Allergies

l. Family history (FH)

## PHYSICAL EXAMINATION OF THE CARDIOVASCULAR SYSTEM

A careful physical examination is a relatively low cost method for an accurate assessment of the cardiovascular system and often provides important information for the appropriate selection of additional tests.

### INSPECTION AND GENERAL CONSIDERATIONS

First, the general physical appearance should be evaluated. The patient may appear tired because of a chronic low cardiac output; the **respiratory rate may be rapid**, indicating pulmonary venous congestion. **Central cyanosis**, often associated with **clubbing of the fingers and toes**, indicates right-to-left cardiac or extracardiac shunting or inadequate oxygenation of blood by the lungs. **Cyanosis** in the distal extremities, cool skin, and increased sweating result from vasoconstriction in patients with severe heart failure. Noncardiovascular details can be equally important. For example, the diagnosis of infective endocarditis is highly likely in patients with **petechiae, Osler's nodes, and Janeway lesions**.

The **blood pressure** should be taken in both arms and with the patient supine and upright; the heart rate should be timed for 1 min. **Orthostatic hypotension and tachycardia** may indicate a reduced blood volume, while **resting tachycardia** may be a clue to the presence of severe heart failure.

Careful examination of the **optic fundi** is essential, and the **retinal vessels may show evidence of systemic hypertension, arteriosclerosis, or embolism**. The latter may result from atherosclerosis in larger arteries (e.g., carotid) or may represent a complication of valvular heart disease (e.g., endocarditis).

**Palpation of the peripheral arterial pulses** in the upper and lower extremities is necessary to define the adequacy of systemic blood flow and to detect the presence of occlusive arterial lesions. It is also important to examine both legs for evidence of edema, varicose veins, or thrombophlebitis. The cardiovascular examination includes careful evaluation of both the carotid arterial and the jugular venous pulses, as well as deliberate precordial palpation

and attentive cardiac auscultation. An understanding of the events of the cardiac cycle is vital to performing an accurate cardiovascular examination.

Note the heart's apical impulses, which are easier to observe in thin individuals and especially in the semi-Fowler position. The point of maximal impulse is notable at the fifth intercostal space and midclavicular line only by thin persons.

### ***Palpation of the Heart***

The location, amplitude, duration, and direction of the cardiac impulse usually can be best appreciated with the fingertips. After observing the cardiac apical impulses, place the patient in the lying position at 45°. Place your hand on patients chest (cardiac area) and note the point of maximal impulse (PM). The normal left ventricular apex impulse is located at or medial to the left midclavicular line in the fourth or fifth intercostal space and is a tapping, early systolic outward thrust localized to a point not more than 3 cm in diameter. It is due primarily to recoil of the heart as blood is ejected and should be evaluated with the patient supine and in the left lateral decubitus position. The PMI are displaced by cardiomegaly, pregnancy, or other chest wall deformities. See Table 3-7 for associated diagnoses and characteristics.

**Tabl. 3-7. Findings on Heart Palpation**

| <b>Increased Force of the Apex</b> | <b>Decreased Force of the Apex</b>                 | <b>Thrill</b>             | <b>Displaced Apex Beat</b>                      |
|------------------------------------|--|---------------------------|---|
| <i>Meaning</i>                     | Decreased cardiac output due to ventricular muscle | it is a palpable murmur   | Apex beat is felt on different place.           |
| <i>Association</i>                 | Cardiomyopathy                                     |                           |   |
| Hyperthyroidism                    | Myocardial infarction                              | Mitral insufficiency      | Pregnancy: Beat felt upward                     |
| Fever                              |  | Aortic stenosis           | and directed to the left                        |
| Pregnancy                          |  | Ventricular septal defect | side  |
| Anemia                             |  |                           | RVH: Beat felt close to the left sternal border |
| Anxiety                            |  |                           |   |

---

RVH = right ventricular hypertrophy. Wery rare condition

**Left ventricular hypertrophy** results in an exaggerated amplitude, duration, and often size of the normal left ventricular thrust. The impulse may be

displaced laterally and downward into the sixth or seventh interspace, particularly in patients with a left ventricular volume load such as occurs in aortic regurgitation and in those with a dilated cardiomyopathy.

Additional abnormal features of the left ventricular apex include marked presystolic distention of the left ventricle, often accompanying a fourth heart sound in patients with an excessive left ventricular pressure load or myocardial ischemia/infarction, and a prominent early diastolic rapid-filling wave, often accompanying a third heart sound in patients with left ventricular failure or mitral valve regurgitation. A double systolic apical impulse is frequently palpable in patients with hypertrophic cardiomyopathy.

**Right ventricular hypertrophy** results in a sustained systolic lift at the lower left parasternal area which starts in early systole and is synchronous with the left ventricular apical impulse. In patients with chronic obstructive pulmonary disease, a right ventricular impulse often may be detected by sliding the fingers up under the rib cage just beneath the sternum. The enlarged right ventricle strikes the ends of the fingertips as an inferiorly directed movement.

**Abnormal precordial pulsations** occur during systole in patients with left ventricular dyssynergy due to ischemic heart disease or to diffuse myocardial disease from some other cause. These pulsations often occur in patients with a recent transmural myocardial infarction and may be present in some patients only during episodes of anginal pain. They are most commonly felt in the left midprecordium one or two interspaces above and/or 1 to 2 cm medial to the left ventricular apex. When a systolic bulge occurs in the region of the apex, it is difficult to distinguish from the impulse of left ventricular hypertrophy.

A left parasternal lift is present frequently in patients with severe mitral regurgitation. This pulsation occurs distinctly later than the left ventricular apical impulse, is synchronous with the v wave in the left atrial pressure curve, and is due to anterior displacement of the right ventricle by an enlarged, expanding left atrium. A similar impulse occurs to the right of the sternum in some patients with severe tricuspid regurgitation and a giant right atrium. Pulsation of the right sternoclavicular joint may indicate a right-sided aortic arch or aneurysmal dilatation of the ascending aorta. Pulmonary artery pulsation is often visible and palpable in the second left intercostal space and may be normal in children or thin young adults. However, this pulsation usually denotes pulmonary hypertension, increased pulmonary blood flow, or poststenotic pulmonary artery dilatation. Abnormally forceful valve closure can be palpated as a tap, and it occurs most commonly in the second left intercostal space in patients with pulmonary hypertension, in the second right intercostal space in patients with systemic hypertension, and at the cardiac apex in patients with mitral stenosis.

**Thrills** are palpable, low-frequency vibrations associated with heart murmurs. The systolic murmur of mitral regurgitation may be palpated at the cardiac apex. When the palm of the hand is placed over the precordium, the thrill of aortic stenosis crosses the palm of the hand toward the right side of the neck, while the thrill of pulmonic stenosis radiates more often to the left side

of the neck. The thrill due to a ventricular septal defect is usually located in the third and fourth intercostal spaces near the left sternal border.

**Percussion** should be performed in each patient to identify normal or abnormal position of the heart, stomach, and liver. However, in patients with a normal cardiac situs, percussion adds little to careful inspection and palpation in the recognition of cardiac enlargement. Carefully percuss the heart area and delineate it, noting any abnormal findings. Pay special attention to any dullness or increase in the cardiac silhouette, which may indicate an increased cardiac size.

*Normal sizes are: right – right parasternal linea, upper – upper edge of 4th costae, left - at the fifth intercostal space and left midclavicular line.*

### **Auscultation of the Heart**

This is one of the best areas for a clinician to analyze and relate directly to the physiology and pathophysiology of the cardiac vascular system. It is not easy to detect small abnormalities on the heart sounds, even for the experienced clinician. There are several diagnostic tools to assess the heart. Before discussing cardiac auscultation, let us review how to use the chestpiece of the stethoscope. There are two types of stethoscopes, one with both bell and diaphragm and another with only a diaphragm. Normally, the bell is used to listen to low-frequency sounds, such as the S<sub>3</sub> and S<sub>4</sub> heart sounds, mitral stenosis, and blood pressure. The diaphragm is useful to listen to high frequency sounds, such as lung and bowel sounds, mitral or aortic insufficiencies, See Table 3-11 for a description of heart sounds. In diaphragm-only stethoscopes, you can alternate both characteristics by alternating from the bell mode to diaphragm mode. For bell mode, just make a contact with the diaphragm on the skin very lightly; to use on a diaphragm mode, press the chestpiece firmly over the skin.

To auscultate the heart, start by auscultating; at the base of the heart (aortic and pulmonic areas) using the diaphragm and then the bell on the specified areas according to Figure 3-5. Normally, S<sub>2</sub> is louder than S<sub>1</sub> at the aortic and pulmonic areas. Examine these areas and then proceed sequentially to examine the fifth left intercostal space, fifth left intercostal space medial to the midclavicular line, tricuspid area, and mitral areas, respectively. Pay attention to any abnormality and concentrate on describing the following parameters:

**Heart rate.** Confirm the heart rate posted on the doors' information sheet if you consider this pertinent.

**Rhythm.** Describe if it is regular or irregular.

**Splitting.** Concentrate on the S<sub>1</sub> sound at the pulmonic and aortic areas (Figure 3-6). Ask the patient/SP to breathe quietly, slowly and steadily.

**TABLE 3-11. Heart Sounds**

| <b>Characteristics</b> |  |
|------------------------|--|
| $S_1$                  | Normal sound caused by the closure of the atrioventricular valves; this is a low-frequency sound that occurs just after the onset of ventricular contraction   |
| $S_2$                  | Normal sound caused by the closure of the semilunar valves; it is a high frequency sound   |
| $S_3$                  | This is a low-frequency sound caused by the rapid passive filling of the left ventricle. It is seen in heart failure and in young healthy <u>athletes</u> . it sometimes indicates a pathology in individuals older than age 40: it is also known as the 'ventricular gallop.'               |
| $S_4$                  | Caused by atrial contraction: seen in the elderly due to a diminished compliance of the left ventricle; also seen in HTN and in CHF (caused by increase in the turbulence of the injected blood from the left atrium to the left ventricle). Pathologic sound known as 'ventricular gallop.' |

CHF = congestive heart failure; HTN = hypertension,

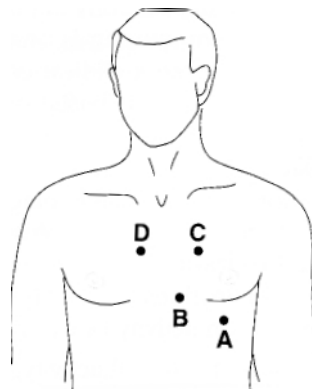


FIGURE 3-5. Heart auscultation areas. A) Apex: good for hearing  $S_1$ , sound and murmurs from mitral valve. B) Lower left sternal border: good for hearing aortic reflux and Tricuspidal reflux. C) Upper Left sternal border: good for hearing  $S_2$ , sound, Pulmonary valve murmur, and ventricular septal defect D) Upper right sternal border: good for hearing left ventricular murmurs (aortic stenosis).

**Location.** Describe where the murmur is maximal.

**Radiation.** Examine the patient's neck and surrounding chest area. Note where the murmur radiates. For example, mitral murmurs radiates to the left axillae.

Other abnormal sounds can occur during the ejection phase (e.g., systolic clicks) or during the diastole (e.g.,  $S_3$ ,  $S_4$ , opening snap), including:

**EJECTION CLICKS.** This is a high-frequency sound that follows shortly after the  $S_1$ .

It is characteristic of pulmonary valve stenosis (pulmonic area). It also occurs in aortic valve disease and dilation of the aorta (aortic area).

**OPENINGS SNAPS.** This is the diastolic sound that occurs during opening of the stenotic valve; it is best heard on the left of the sternum.

**MIDSYSTOLIC CLICK** is associated with mitral valve prolapse and may be accompanied with late systolic murmur.

Maximizes are sounds produced by the increase on the turbulent flow that occurs by the passage of blood through anatomic defect. Both systolic and diastolic murmurs can be described as early, mid, and late. Also, systolic murmurs that are heard throughout the systole are called pansystolic or holosystolic. Late diastolic murmurs may be called presystolic murmurs. It is very important to know how to grade murmurs. If you have a patient with a murmur, you must describe the grade of the murmur in your notes. The **grading/intensity** of murmurs are denoted on a scale from 1 to 6:

**Grade 1:** Difficult to hear

**Grade 2:** A quiet murmur, but audible with stethoscope

**Grade 3:** Easy to hear with stethoscope

**Grade 4:** Loud, obvious murmur; a thrill can be palpated

**Grade 5:** Very loud, heard not only on the precordium

**Grade 6:** Heard without stethoscope

**Innocent murmur** is a term used for murmurs in children and in young adults or athletes. They are characterized by being quiet (normally less than grade 3) and by not being related to ventricular hypertrophy or other heart sounds. Pulses, chest x-rays, and ECG are normal. An innocent murmur is best heard at the left sternal edge.

## VALVULAR HEART DISEASE

**Mitral stenosis.** *Diastolic  $S_2$  murmur (or thrills) with MP at apex of the heart. Systolic click. Accent of second ton on pulmonary artery. Hypertrophy of left atria.* The echocardiographic appearance of a restricted valve opening, due to leaflet thickening and commissural fusion, and of shortened, thickened chordae is virtually diagnostic of rheumatic deformity (Planimetry of the mitral area in the diastolic short-axis view and evaluation of the rate of falloff of the estimated transmitral diastolic pressure gradient by Doppler permit quite reliable estimation of valve area. Using the Doppler technique, mitral valve area (MVA) in square centimeters can be estimated with the equation  $MVA = 220$  divided by duration of time (in milliseconds) necessary for the peak diastolic pressure gradient to decrease by 50 percent. Other causes of inflow obstruction, such as atrial myxoma (Fig. 190-4, right) or thrombus, massive annular calcification, supravulvar ring, cor triatriatum, and parachute mitral valve also may be detected.

**Mitral regurgitation.** *Systolic  $S_{2-3}$  murmur with MP at apex of the heart. Weak 1 ton. Accent of second ton on pulmonary artery. Hypertrophy of left ventricle.* Systolic mitral competence depends on normal function of the mitral leaflets and their supporting structures, including the annulus, chordae

tendineae, papillary muscles, and surrounding myocardium. Two-dimensional transthoracic or transesophageal techniques are useful for recognizing the etiology of mitral regurgitation, which includes rheumatic disease, prolapse, flail leaflets resulting from chordal or papillary muscle rupture, annular calcification, atrioventricular canal defects, myxomas, endocarditis, hypertrophic cardiomyopathy, and ventricular dysfunction. Doppler mapping provides a gross estimate of the severity of regurgitation.

**Aortic stenosis.** *Systolic S<sub>3-4</sub> murmur with MP at bottom of the heart. Splitting of second ton. Hypertrophy of left ventricle.* Subvalvular, valvular and supra-valvular obstruction can generally be detected by two-dimensional echocardiography. Systolic leaflet doming and an unusual number or size of cusps (two in a bicuspid valve) suggest congenital valve disease. Acquired fibrosis and calcification cause valve thickening. Doppler detection of high-flow velocity across the valve, corresponding to a high transvalvular gradient, indicates the presence of stenosis. Lesser flow velocities do not, however, exclude stenosis because both reduced stroke volume and inability to position the Doppler beam parallel to flow may appreciably decrease measured velocities. If velocity can be reliably measured, aortic valve area (AVA) can be quantitated.

**Aortic regurgitation.** *Dyastolic S<sub>1-2</sub> murmur with MP at bottom of the heart. Hypertrophy of left ventricle.* Dilatation of the aortic root and aortic dissection can be distinguished from valve leaflet abnormalities causing regurgitation, including congenital disease, sclerosis, endocarditis, prolapse, and flail cusps. The presence and spatial extent of regurgitation is evaluated by Doppler study.

**Prosthetic valves** Mechanical prostheses are difficult to evaluate, because their intrinsically high echogenicity often interferes with recognition of valve motion, vegetations, thrombi, and regurgitation. Abnormalities of bioprostheses, including fibrosis, calcification, vegetations, tears, and regurgitation, are more easily recognized. Transesophageal echocardiography should be considered strongly in patients with suspected prosthetic mitral valve dysfunction when transthoracic evaluation is nonrevealing. Angiography and hemodynamic study may be necessary for full evaluation.

It is very important to make a clinical correlation of the patient. You are not expected to make a clinical diagnosis based only on the auscultation. The doorway information sheet and the general medical history from the SP are important information that give you a broad idea of several possible diagnoses. Remember, be prepared to answer an SP's questions about possible diagnoses and prognosis. Never give false reassurance to a patient; be sincere and professional.

Heart disease can be classified by the patient's symptoms and by following the New York Heart Association Functional Disability Grading System. This classification serves to quantify the limitation on activity of cardiac patients.

**Class I:** limitation of physical activity. Ordinary physical activity does not cause Tattgue, dyspnea, or anginal pain.

**Class II:** Slight limitation with mild to moderate activity (e.g., walking more than 2 blocks), but no symptoms at rest

**Class III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity (e.g., walking less than 2 blocks) cause symptoms (e.g., dyspnea, pain).

**Class IV:** Symptoms at rest or with minimal activity, and symptoms of frank congestive heart failure.

Cardiovascular disease causes 1 million deaths yearly, and half of these are due to coronary artery disease (CAD). It is very important to document information about the patient's risk factors for CAD. Prevention of risk factors can be primary or secondary. Primary prevention involves the intervention on the modifiable risk factors before the onset of the disease. For example, for patients who smoke, encourage and counsel them to quit. Help them set a quit date, provide self-help materials, and set up follow-up visits to assess compliance. Secondary prevention involves the intervention after the onset of the disease.

#### **TABLE Risk Factors for Coronary Artery Disease**

| <b>Modifiable Risk Factors</b>         | <b><u>Nonmodifiable</u> Risk Factors</b> |
|--|--|
| <u>Cigarette smoking</u>               | <u>Positive family history</u>           |
| <u>Increased LDL and decreased HDL</u> | Gender                                   |
| <u>Increased serum cholesterol</u>     | Age                                      |
| <u>Hypertension</u>                    |  |
| <u>Diabetes mellitus</u>               |  |
| <u>Estrogen deficiency</u>             |  |
| Inactivity                             |  |
| Obesity                                |  |

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

### **Syndromes in cardiology**

**1. Sudden death** - Cardiac Arrest - *Absent or inadequate ventricular contraction that immediately results in systemic circulatory failure* cardiac arrest is a medical emergency that overrides all others except exsanguinating external hemorrhage or airway obstruction, which should be controlled simultaneously. Unless rapidly corrected, cardiac arrest is rapidly fatal. In approximately 5 percent of sudden cardiac deaths, no demonstrable anatomic abnormality is found.

**2. Stenocardia – Angina Pectoris** A clinical syndrome due to myocardial ischemia characterized by precordial discomfort or pressure, typically precipitated by exertion and relieved by rest or sublingual nitroglycerin.

**3. Cardialgia**, also called **cardiodynia**. Any pain in the region of the heart. The term is used even if the heart is not directly involved

**4. Myocardial infarction (MI), heart attack**, a blockage of a heart artery. It is caused by a kind of hardening of the arteries (atherosclerosis) or a blood clot. This

results in a **dead tissue area in the heart muscle**. Myocardial infarction often begins with a crushing, viselike chest pain that may move to the left arm, neck, or upper abdomen. It sometimes seems like indigestion or a gallbladder attack. The patient becomes ashen, clammy, short of breath, faint, anxious. The patient may feel that death is near. Typical signs are rapid heartbeat, a barely felt pulse, low blood pressure, above normal temperature, and heartbeat irregularities.

**5. Arrhythmias:**

**6. Congestive Heart Failure:** A complex clinical syndrome that results when the heart is unable to pump an adequate supply of blood to meet the body's metabolic needs, leading to inadequate tissue perfusion; vascular, cardiac, and pulmonary congestion; and diminished functional capacity.

**a) Left ventricle failure:** Tachycardia, fatigue and dyspnea on exertion, intolerance to cold, cough, blood tinged sputum, restlessness, paroxysmal nocturnal dyspnea, insomnia, crackles and wheezes in the lungs, ventricular and atrial gallops

**b) Right ventricle failure:** Fatigue, fullness in the neck and abdomen, ankle swelling, distention of neck veins, weakness, anorexia, nausea, liver enlargement, nocturia, ascites, tricuspid murmur

**Potential Complications** *Acute pulmonary edema* occurs with acute heart failure and is manifested as extreme dyspnea, cyanosis, hyperpnea, and plunging oxygen saturation. Death occurs if the condition is not treated immediately.

**7. Hypertension, high blood pressure,** a common disorder, often without symptoms marked by high blood pressure persistently exceeding 140/90. Essential hypertension, the most frequent kind, has no one known cause, but the risk of it is increased by overweight, a high sodium level in the blood, a high cholesterol level, and a family history of high blood pressure. Known causes of hypertension include adrenal problems, over-active thyroid gland, certain pregnancies and kidney disorders. Hypertension is more common in men than in women and is twice as great in blacks as in whites. Persons with mild or moderate hypertension may have no symptoms or may experience headaches, especially on rising, ringing in the ears, lightheadness, easy fatigability, and the feeling that their heart is beating wildly. With sustained hypertension, artery walls become thickened and resistant to blood flow, and, as a result, the blood supply to the heart may be reduced causing angina or heart attack. High blood pressure is often accompanied by anxiety attacks, rapid or irregular heart beat, profuse sweating, pallor, nausea, and, in some cases, fluid in the lungs. Malignant hypertension, marked by a diastolic pressure higher than 120, severe headaches, blurred vision, and confusion, may result in heart attack or stroke.

**8. Syncope - syncope** It usually follows a feeling of lightheadedness and may often be prevented by lying down or by sitting with the head between the knees. It may be caused by many different factors, including emotional stress, pooling of blood in the legs, heavy sweating, or sudden change in room temperature or body position

9. **Collapse**, . an abnormal condition marked by shock MAP < 100 mm Hg
10. **Shock** - hypotension < 90 mm Hg with renal failure, respiratory failure, microcirculation blockade, confugen, syncope, death.

### Study question

1. While taking a PMH, the clinician learns that a patient is taking digoxin, a cardiac medication. The clinician should
  - (A) list the digoxin in the PMH
  - (B) find out about the cardiac symptom and put it in the PMH
  - (C) find out how long the patient has been taking the digoxin
  - (D) find out about the cardiac symptom and put it in the ROS
  - (E) find out about the cardiac symptom and put it in the HPI
  
2. The patient complains that; the pain starts when doing aerobics, lasts for 10 minutes, is like a dull, achy pressure, occurs nightly, two or three times a week for the past 3 weeks, The pain increases if the patient does not stop aerobics. That pain is:
  - A. Stenocardia
  - B. Myocardium Infarction
  - C. Chest radiculitis
  - D. Other neurologic disorder
  
3. In preparing a problem list for a new patient with a proven myocardial infarction, all of the following information should be relegated to the inactive problem list EXCEPT
  - (A) hysterectomy, 1976
  - ( B ) diabetes mellitus
  - (C) x-ray confirmed duodenal ulcer, 1984
  - (D) right hip fracture, 1988
  - ( E ) pneumococcal pneumonia, 1989
  
4. An appropriate screening test for a 40-year-old asymptomatic man who **presents for** a health evaluation is
  - (A) hemoglobin and hematocrit,
  - (B) serum cholesterol
  - (C) thyroid function tests
  - (D) serum electrolytes
  
5. The patient is a 55-year-old woman with diabetes and coronary artery disease. She continues to work at her secretarial position at an insurance company and lives with her husband in a two bedroom apartment. She is fatigued easily and takes frequent naps. She appears alert and well nourished. The above description includes all of the following factors EXCEPT

(A) diagnosis (B) prognosis (C) symptoms (D) ADLs ( E ) signs

### Questions 6-10

For each clinical situation described below, select the single most useful laboratory test.

(A) EKG

( B ) Chest x-ray

(C) CBC

(D) Echocardiogram (E) None of the above

6. A 33-year-old lawyer with cough, fever, and pleuritic chest pain of 3 day's duration

7. A 62-year-old male construction worker with a 2-hour history of crushing substernal chest pain

8. A 23-year-old student with sudden onset (1 hour ago) of left sided chest pain and shortness of breath. Found to have absent breath sounds over the left hemithorax

9. A 40-year-old woman with a 3-hour history of "palpitations" who is found to have a heart rate of 160/min

10. A 72-year-old woman with a diffuse petechial rash

### Answers and explanations

**1. The answer are: *The answer E.*** Any problem or symptom for which patients are currently being treated should be included in the HPI and have the seven parameters determined. Digoxin is a cardiac medication that cannot be forgotten and put in the PMH. Any cardiac symptom needs to be uncovered and reported in the HPI.

**2. The answer is A.** The pain that occurs when patient doing exersises, lasts seven minutes, is like a dull, achy pressure, occurs nightly, increases if the patient does not stop aerobics is stenocardia.

**3. The answer is B.** The presence of diabetes must be kept in mind at all times in the management of the patient, regardless of the nature of the presenting problem. The hysterectomy and hip fracture are legitimate inactive problems and of no concern now, but they must remain as part of the patient's comprehensive medical history. The duodenal ulcer may recur, so it must be noted. The pneumonia is not a problem now, but since pneumococcal disease *may* indicate a specific lack of resistance to this organism, it must be carried forward on the inactive problem list.

**4. The answer is B.** The only blood test recommended for both men and women at any age is a serum cholesterol obtained every 5 years. Hemoglobin and hematocrit are not warranted for men but may be important in menstruating women. Thyroid function tests are unnecessary on asymptomatic men but may be tested in asymptomatic older women. Serum electrolytes are never recommended as a

routine. Fasting serum glucose is also not recommended routinely and should be ordered only if symptoms warrant it.

**5. The answer is B.** Symptoms are any problems experienced by the patient, which may be used to identify the underlying pathology. Signs are physical indications of the disease, which may be visible to anyone or specifically to the clinician. Diagnosis is the underlying cause of any signs or symptoms. ADLs are a measure of a patient's level of functioning. Prognosis is the predicted course of a disease or condition.

**6-10. The answers are: 6-B, 7-A, 8-B, 9-A, 10-E.**

**6. 'B'** The combination of symptoms, such as cough, fever, and pleuritic chest pain, in a young person are highly suggestive of pneumonia, a diagnosis best confirmed by chest x-ray.

**7. 'A'** Crushing substernal chest pain is the classic symptom of myocardial infarction. The EKG may be definitive and, if not, is certainly essential to monitoring the course of the illness or beginning the process of "ruling out" the most dangerous diagnostic possibility.

**8. 'B'** The combination of historical data and physical findings (i.e., sudden onset of shortness of breath) are most consistent with spontaneous pneumothorax. It is essential for the proper care of the patient to establish that pneumothorax is present and to determine the degree of the lung compromise.

**9. 'A'** A heart rate of 160/min demands a definition of the conduction problem present. The proper choice of therapeutic intervention requires a knowledge of the source of the tachycardia (atria) or ventricular), which can usually be defined from a rhythm strip or a 12-lead EKG.

**10. 'E'** Petechial rashes are secondary to platelet problems until proven otherwise. This woman's problem may be either inadequate platelet numbers or dysfunction of platelets. The most important test in this situation is a platelet count.

**4**

## **The Gastrointestinal System Examination**

The GI system is an important system that mandates special attention to symptoms. Common symptoms related to the GI system are **abdominal pain, dyspepsia, nausea and vomiting, diarrhea, dysphagia, hiccups, constipation and signs related to GI bleeding (e.g., hematemesis, hematochezia, and melena).**

### **DIFFERENTIAL DIAGNOSIS OF THE ABDOMINAL PAIN**

The abdominal cavity has several organs, and there is no pathognomonic sign or symptom that is specific to each abdominal organ. Frequently, the signs and symptoms overlap each other, so it is very important to consider a wide possibility of diagnoses. Other disease factors, such as age, gender, and other risk factors, are very important to consider case by case. Abdominal pain is a common complaint. The anatomic localization, quality, frequency, and form of pain presentation may orient you toward the diagnosis. Knowing the origin of abdominal pain is

useful to understanding the differential diagnosis. As a general rule only, only three processes are capable of producing pain on the alimentary tract:

**1. Pain caused by tension-e.g.,** powerful peristalsis caused by oxalic acid, infection, and so forth

**2. Pain caused by ischemia-e.g.,** strangulation, obstruction, adhesion, volvulus

**3. Pain caused by peritoneal inflammation** (peritonitis)

Acute abdominal pain and colic type pain may be due to cholecystitis, ureteral stones, intestinal obstruction, and so forth.

Only a minority of patients presenting with acute abdominal pain are found to have a problem that requires surgical treatment. It is very important to remember that almost 50% of these patients have no identifiable causes of abdominal pain. Other conditions that do not require surgical treatment include gastroenteritis, pelvic inflammatory disease (PID), UTI, and ureteral stone. On any presented case with abdominal pain, it is important to consider the possibility of pneumonia; some basal lung pneumonias may cause a referred pain to the abdomen.

**Dyspepsia** is an imprecise term to describe an upper abdominal discomfort, such as epigastric tenderness, fullness sensation, bloating, early satiety, heartburn, or regurgitation. The differential diagnosis of dyspepsia is listed in Table 3-22. **Nausea** and **vomiting** are symptoms that may involve more than a GI system abnormality. Systemic illness (e.g., CNS disorders), side effects of medications, and some viral illnesses may cause nausea and vomiting. Also, nausea and vomiting are common symptoms of pregnancy. If intestinal obstruction is not suspected, common antiemetics and oral intake limited to clear fluids are helpful to control it.

**Diarrhea** can be classified as acute or chronic. The approach to a patient with diarrhea consists of trying to identify and treat the possible cause, control any fluid and electrolyte abnormality and, if indicated, use of antidiarrheal medications. Table 3 provides a classification and etiologic differential diagnosis of diarrhea. Esophageal diseases are commonly manifested by dysphagia, odynophagia, or heartburn. **Dysphagia** is a difficulty in swallowing and is commonly described as a sticking sensation. **Odynophagia** is pain on swallowing. It is important to know if dysphagia is for solids or liquids. **Heartburn** is described as substernal burning sensation that radiates toward the mouth and is increased by bending forward. **Hiccups** are a sporadic and unremarkable symptom that generally does not mandate medical consultation. However, chronic, recurrent hiccups may indicate a severe condition that mandates further examination. **Constipation** is a common complaint that you may be presented with during the CSA exam. Constipation can have several causes, such as lack of medications (e.g., aluminium hydroxide, anticholinergics, iron supplements, narcotics, antihypertensives), or systemic diseases (e.g., hypothyroidism, diabetes,

hypercalcemia). It is important to question the patient about the presence of tenesmus (pain during the defecation), which may indirectly cause constipation. Ask about and document any change in the pattern of stools, including consistency, thickness, or presence of blood. Colon cancer always needs to be considered.

Finally, it is very important to consider the evaluation of a patient with **GI bleeding**. Hemodynamically unstable patients are treated initially by maintaining an adequate circulatory volume, and their initial assessment is oriented initially toward monitoring the heart rate, blood pressure, urinary output, postural changes, and so forth. Nonacute GI bleeding can be evaluated in the office and can be classified as upper or lower GI bleeding, depending on the signs and symptoms.

Upper GI bleeding may be suggested by the presence of **hematemesis** or **melena**. When hematemesis is referred, upper airway sources or hemoptysis must be ruled out. The approach to those patients depends on the patient's stability, the rate of blood loss, procedural availability, and local expertise.

Lower GI bleeding can be referred as **hematochezia** or brisk blood in feces, or can be suggested during positive Guaiac test (i.e., hemocultpositive stool test). Remember, this test may have false-positive results due to certain foods (e.g., broccoli, radishes, turnips, roast beef) and medications (e.g., Pepto-Bismol).

A Gregersen test can be performed quickly in a routine office visit.

## **PHYSICAL EXAMINATION of the gastrointestinal system**

The correct order to examine the **Gastrointestinal System** is **inspection, auscultation, percussion, and palpation**. The medical history is the most important tool in the study of patients with GI problems. Always accompany the GI exam with the palpation of the supraclavicular nodes and axillary nodes. As mentioned, the presence of palpable left supraclavicular node (**Virchow node**) and left axillary node (**Irish node**) always alerts you to the possibility of GI cancer.

### **INSPECTION**

Observe the skin and note the presence of any abnormality, such as rashes, purpura, or evident hernias.

**striae gravidarum**, uneven furrows, red to purple in color, that appear in the skin of the stomach, thighs, and buttocks of pregnant women.

On thin individuals, you may notice the pulsation of the abdominal aorta on the midline above the umbilicus, and sometimes the periodic rippling movement of the peristaltic movement on intestinal obstruction. Note the gravidae striae in

women as well as the purple striae in patients with Cushing syndrome. Ascitic patients may present with a typical globular abdomen.

Examine the skin for the presence of: **Grey Turner sign** is a bluish discoloration of either flanks seen in pancreatitis. **Cullen sign** is a bluish discoloration seen on the periumbilical area in pancreatitis.

**Caput medusa sign** is visible vascular veins observed around the umbilicus, seen in liver cirrhosis. Always describe your findings by dividing the abdomen in four quadrants with imaginary lines that crosses at the umbilicus. Figure 3-8 shows you two types of abdominal divisions.

## AUSCULTATION

Start by placing the diaphragm of the stethoscope on the abdomen, and listen carefully to the bowel sounds. The normal bowel sounds (gurgling sounds) vary from 5 to 34/min in frequency, depending on the dynamic state of the bowel. The peristaltic sounds occur at 5 to 10 second intervals. An increase in frequency of bowel sounds can be caused by inflammation of the intestinal mucosa due to infections or inflammatory disorders, such as Crohn disease and ulcerative colitis. If your patient has hypertension, it is important to listen at the level of the epigastrium (2.5 cm above laterally to the umbilicus) to attempt to detect renal arterial bruits that can be caused by atherosclerotic disease, congenital renal artery disease, or fibromuscular hyperplasia. Auscultate over the liver and the spleen areas. The presence of a soft bruit over the liver is always pathologic and may suggest either hepatitis or primary liver cell *carcinoma*. You may note a friction rub over the left hypochondrium in splenic infarction. Occasionally a rub over the spleen maybe heard, which may suggest an inflammation in the capsule.

## PERCUSSION

This procedure is important for delineating the liver and spleen areas. Also, it is useful to identify the presence of ascitic fluid and solid or fluid-filled masses. You may alternate percussion with palpation. Start by percussion lightly in all four quadrants to determine the distribution of the gas in the abdomen. If you suspect ascites on the patient, place him or her in a supine position. The normal gas distribution on this position is to float above the ascitic fluid. As you percuss over the abdominal wall, you will notice the change of the percussion sound from tympanic or resonant to dull on the lateral sides. Mark the skin at the fluid gas level detected, then roll the patient to one lateral side and note the change of the position of the dullness and tympani. Mark the skin again

## **PALPATION**

This part of the abdominal examination can be divided into light and deep palpation.

### ***Light Palpation***

This procedure is particularly useful for detection of muscular resistance and abdominal tenderness and for exploration of superficial subcutaneous masses. Start by asking the patient to show you the area of pain or tenderness if abdominal pain is a presenting complaint. If the patient has a more localized pain, tell him to point to the area of pain with his finger. Begin light palpation in the area adjacent to tenderness site and then continuing to previously specified region (area of tenderness or pain).

### ***Deep Palpation***

Deep palpation is usually required to delineate the abdominal organs (liver, spleen, and kidneys) or other pathologic masses. Localize the anatomic area where the pain is referred by the patient, and cautiously make soft and light pressure. As you palpate the patient, try to imagine which organ is the cause of the problem. Initially the visceral pain (due to affection of the visceral peritoneum) will be referred to other regions distant from the original site of problem; as the inflammatory or irritative process continues, the parietal peritoneum become affected and the pain becomes somatic and then well-localized. As explained, the pain of appendicitis is initially referred in the epigastrium and/or in the periumbilical area, then may progress to be localized on the right lower quadrant (RLQ). If you have a patient with consistent symptoms of appendicitis, perform three following maneuvers:

### **REBOUND TEST**

This maneuver can be performed by making a soft continuous pressure on testing area followed by a sudden inadvertent removal of the hand. If this procedure exacerbates pain, it constitutes the **rebound sign**. Rebound sign is indicative of peritoneal inflammation, and it can be associated with appendicitis, tubal pregnancy, pelvic inflammatory disease, and ruptured ovarian follicle.

### **Psoas TEST**

For suspected appendicitis, have the patient lie down and then place your hand just above the patient's right knee; ask the patient to flex his leg at the hip against your resistance. An increase of pain on the RLQ constitutes the **Psoas sign** and is indicative of an inflamed appendix. This procedure is positive when the appendix is in retrocolic position adjacent to the iliopsoas muscle. Assess the patient by asking him if he can raise his legs while you oppose resistance over his knee.

### **OBTURATOR TEST**

With the patient in the same position for the Psoas test, flex the same right hip with the knee flexed (bent) and rotate internally or externally. A RLQ pain constitutes a positive **obturator sign**.

## **Rovsings SIGN**

This test is positive when the patient complains of pain in RLQ at the moment of soft continuous compression of lower left quadrant (LLQ).

It is important to remember that all of these signs may be absent if the appendix is on anterior position or is wrapped in an inflammatory mass (phlegmon or omentum). The physical exam of a suspected patient with appendicitis can not be considered completed without performing a rectal or pelvic examination. Pain is also exacerbated on those maneuvers.

If you find a mass during abdominal palpation (less probable), note the location, size, shape, consistency, adherence, tenderness, and so forth.

Normally, the abdominal aorta is felt as a discrete pulsatile structure over the midline above the umbilicus; a large pulsatile mass on this localization may be indicative of aortic aneurysm. In 95% of cases, aortic aneurysms are asymptomatic; causes include atherosclerosis, trauma, infection, and syphilis. Evaluate by ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), and aortogram. If you suspect an aortic aneurysm, check the peripheral pulses in the lower extremities; the extremities may look pallor, may feel cool, and the pulses may be diminished or unequal.

The liver and gall bladder must be explored by palpating the right upper quadrant (RUQ) using both hands or by the bimanual manner (placing one hand behind the patient and the other over the abdomen). Always talk with the patient, explaining every procedure that you are going to do. Looking to his head, proceed to delineate the upper and lower margin by palpation and percussion. ***The liver's normal sizes are 6 to 12 cms at the right midclavicular line and 4 to 8 at the midsternal line.***

***Describe any abnormal characteristic, such as tenderness or nodularity.***

Depending on your clinical suspicion, correlate your exam with other clinical data (e.g., jaundice tremors, upper GI bleeding, loss of hair on extremities, alteration on the mental status if you are suspecting liver cirrhosis, etc.). Ask the patient to take a deep breath as you try to palpate the lower margin of the liver and the gall bladder. The normal gall bladder is not palpated, but when obstructed and distended with bile, it can be detected on palpation. Determine the presence

**Murphy sign** Murphy sign is characterized by the arrest of inspiratory effort as the examiner's hand contacts the inflamed gall bladder.

There are many signs that can be related to liver and gall bladder disease.

**Jaundice** is one of the most reliable and one of the first that the clinician frequently attributes. The differential diagnosis of jaundice is wide and may indicate more than liver diseases. Table 3-18 shows the differential diagnosis of jaundice.

Palpation of the spleen is similar to the liver, and under normal conditions the spleen will not be palpated.

## **Main syndromes of gastro-intestinal system diseases**

1. **Abdominal pain:** gastritis, peptic ulcer, cholecystitis, pancreatitis, appendicitis, hernia, pneumonia, myocardium infarction, diabetic ketoacidosis, vasculitis.
2. **Gastro-intestinal bleeding**
3. **Jaundice:** hepatic, posthepatic (mechanical), haemolytic
4. **Hepato-cellular insufficiency**

## Case

**A 54-year-old white man presents to his general practitioner's office complaining of fatigue. He says that he tires easily and often feels light-headed and short of breath after climbing a single flight of steps or taking a short walk. He says that he is having difficulty at work because he is "just not himself",**

## QUESTIONS

- *What are some possible causes of generalized fatigue and weakness?*
  - *What other questions would you like to ask this patient?*
- DISCUSSION**

Fatigue and weakness are common complaints that can be psychogenic or physical in origin. It is important to differentiate between these broad etiologic categories. Psychogenic causes consist of anxiety states and depression. Physical causes include infectious disease, metabolic disorders, blood dyscrasia renal disease, liver disease, chronic pulmonary disease, chronic cardiovascular disease, neoplastic diseases, and neuromuscular disease. Specific examples of these physical causes of fatigue include tuberculosis, diabetes mellitus, hypothyroidism, hyperparathyroidism, Addison's disease, anemia, lymphoma leukemia, acute and chronic renal failure, acute and chronic hepatitis, cirrhosis, and common neoplastic diseases such as carcinoma of the lung, breast, colon, pancreas, prostate, ovary or endometrium.

To narrow the diagnostic possibilities for this patient's fatigue and weakness, additional history should be obtained. The patient should be questioned about whether he has experienced weight loss, fever, chills, chest pain, paroxysmal nocturnal dyspnea, orthopnea, pedal edema, abdominal pain, changes in bowel habits, melena, hematochezia, polyuria, polydipsia, polyphagia, intolerance to heat or cold, insomnia. A positive answer to these questions often, although not always, would indicate a physical organic cause of fatigue or weakness.

**Further history reveals that the patient's symptoms started about 2 months ago and have steadily worsened. He claims he was in excellent health until this time; in fact, he has not had a routine physical exam in about 2 years because he has felt healthy. The patient takes no medications, except for the occasional use of acetaminophen or laxatives. He is an executive in a publishing company**

who smokes about half a pack of cigarettes a day and drinks a martini or two at lunch. He has no significant family history except that an estranged older brother died after an abdominal operation for an unknown cause. The patient denies chest pain or palpitations but has occasional shortness of breath and dyspnea on exertion as described above. He has had no loss of appetite and even jokes that he can eat even on days when he is a bit "irregular." When asked about his constipation, he notes that he sometimes has difficulty passing his stool, but the stool is of normal consistency. He also reports that his stools have seems bit darker lately, but he thought it might be due to laxatives he took for constipation; he has not noticed any bright red blood in the stool and denies hematemesis, nausea, vomiting, or diarrhea.

## QUESTION

- *Which of these signs and symptoms concern you?*

Physical examination reveals a well-developed, overweight white man with a somewhat rapid respiratory rate (i.e., 20 respirations/min). Other vital signs show a pulse of 94 bpm, a blood pressure of 110/60 mm Hg, and a normal temperature. His skin is pale, as are his mucous membranes. His lungs are clear upon auscultation and his heart rhythm is regular, with a normal first and second heart sound (S<sub>1</sub> and S<sub>2</sub>) and no third or fourth heart sound (S<sub>3</sub> or S<sub>4</sub>). His abdomen is soft, without tenderness or obvious masses. His extremities show no cyanosis or edema; he has prolonged capillary refill. His rectal exam shows no palpable masses and dark, heme-positive stool.

## QUESTIONS

- *Based on this physical examination, what do you suspect is the cause of this man's fatigue?*
- *What are some of the causes of melena?*
- *What sorts of disorders produce hematochezia?*
- *How would you proceed in working up the heme-positive stool?*

A nasogastric tube is inserted but does not reveal any evidence of blood. The physician has an anoscope in his office, but anoscopy does not reveal any obvious lesions. In-office hemoglobin and hematocrit tests reveal values of 9.4 g/dl and 36%, respectively. The physician decides to refer the patient immediately to a gastroenterologist for further workup of his gastrointestinal bleeding.

## QUESTIONS

- *Why does the physician first look for evidence of upper gastrointestinal bleeding?*

- *What are the most common causes of lower gastrointestinal bleeding in this age-group?*

The gastroenterologist sees the patient immediately, and some laboratory tests are performed. A complete blood count (CBC) reveals a white cell count of  $7.2/\mu\text{l}$ , a platelet count of  $525,000/\mu\text{l}$ , and hemoglobin and hematocrit consistent with the previous values. Red cell indices show a mean corpuscular volume (MCV) of  $70 \mu\text{m}^3$  and a mean corpuscular hemoglobin (MCH) of 25 pg. Serum iron and transferrin are decreased. Prothrombin time (PT) and partial thromboplastin time (PTT) are normal, as are electrolyte, blood urea nitrogen (BUN), and creatinine levels.

## QUESTIONS

- *What type of anemia do these values suggest?*
- *Which of the previously mentioned differential diagnoses can be ruled out by the laboratory value,*
- *What conditions are the highest on your differential?*
- *What are your immediate management plans?*

the gastroenterologist arranges for a colonoscopy. During the colonoscopy, several polyps are noted in the descending portion of the colon. The polyps are 1-2 cm in size, and most are pedunculated. These lesions are removed by snare cautery and sent to pathology for diagnosis.

## QUESTIONS

*What other procedures could have been employed to investigate this problem? o Why was colonoscopy useful in this case? s What would have prevented colonoscopy from being a useful diagnostic tool?*

pathology reveals villous adenomatous polyps with no foci of carcinoma. The patient is reassured and told to return in 1 year for a follow-up colonoscopy. If unremarkable, a repeat colonoscopy at 3 years would be indicated.

**Study question**

The clinician is sent to the hospital ward to do a workup on a newly admitted 32-year-old patient with the CC of abdominal pain and a working diagnosis of acute pancreatitis.

1. The primary data base should include all of the following information EXCEPT

- (A) complete medical history
- ( B ) physical examination
- C) working problem list
- (D) tentative plan
- ( E ) final diagnosis

2. The most important part of the physical examination on this patient is the abdominal assessment. All of the following maneuvers are likely to yield useful information EXCEPT

- (A) palpation of the liver
- ( B ) palpation of the gallbladder
- (C) palpation for upper abdominal tenderness
- (D) palpation of the abdominal aorta
- ( E ) assessment of the bowel sounds

3. The clinician finds diffuse abdominal tenderness and guarding on examination as well as a liver span of 18 cm. The problem list should include all of the following conditions EXCEPT

- (A) possible alcohol abuse
- ( B ) abdominal pain
- (C) acute pancreatitis
- (D) abdominal tenderness and guarding
- ( E ) hepatic enlargement

4. 8. The clinician is asked to present this case to the ward attending. The presentation must include all of the following information EXCEPT the

- (A) HPI
- ( B ) alcohol consumption history
- (C) patient's vital signs
- (D) FH of alcohol consumption
- ( E ) abdominal examination findings

**Questions 5-8**

For each of the case scenarios presented below, choose the most likely body system implicated.

- (A) Musculoskeletal
- (B) Renal-urinary
- (C) Respiratory
- (D) Reproductive

## (E) Gastrointestinal

5. A 23-year-old runner comes to the outpatient department with a complaint of persistent pain in the left knee and calf since Sunday's marathon.
6. A 72-year-old hypertensive man comes into the emergency room with acute shortness of breath, cyanosis, and rales throughout both lung fields.
7. A 32-year-old woman who has been taking high doses of calcium to prevent osteoporosis comes in with a 2-hour history of excruciating left flank pain.
8. A 25-year-old man comes to the clinic with a 3-day history of 10-12 loose stools a day, which began while he was camping in the Rocky Mountains.
9. In what order should the abdominal examination sequence proceed?
  - i A) Inspection, auscultation, palpation, percussion (B) Inspection, palpation, auscultation, percussion (C) Inspection, palpation, percussion, auscultation (D) Inspection, percussion, auscultation, palpation (E) Palpation, auscultation, inspection, percussion.
10. The effectiveness of the spleen examination is improved by all of the following factors EXCEPT
  - (A) a thin patient
  - (B) asking the patient to take slow deep breaths
  - (C) advancing the examiners fingers on expiration
  - (D) asking the patient to roll on the left lateral decubitus
  - (E) asking the patient to place his or her left hand under the left buttocks.

**Answers and explanations**

1. **The answer is E.** [*Chapter 10 ll; IV A 1*] The data base always includes a complete medical history, physical examination, problem list, and usually a preliminary plan. The primary data base should never include a definitive diagnosis because the supporting data have not been obtained. It is potentially hazardous to jump to a final diagnosis as a part of primary data collection.
2. **The answer is D.** [*Chapter 6 ll OJ*] The probability of a 32-year-old having abdominal aortic disease as the basis for his abdominal complaints is remote. On the other hand, general assessment for signs of acute inflammation or viscus perforation are rational and essential. For further information on assessment for the complaint of abdominal pain, see any standard surgical textbook.
3. **The answer is C.** [*Chapter 10 ll A*] At this stage of the data collection, symptoms and signs are known at a level that does not allow a diagnosis. The problems should be listed at the level at which they are absolutely definable.
4. **The answer is D.** [*Chapter 11 VII C, D*] The oral case presentation should include all of, but no more than, the data necessary for resolution of the patient's immediate problems. The FH of alcohol consumption is a second level of information, which is not critical to the immediate management of the acutely ill person being discussed.

**5-8. The answers are: 5-A, 6-E, 7-B, 8-E.** Young adult~, are commonly seen for traumatic injuries to the muscles and joints, especially those individuals who are strenuously physically active. The temporal relationship to the marathon should alert the clinician to the high probability of a musculoskeletal problem.

Despite the fact that this 72-year-old man presents with what appear to be respiratory problems, the history of hypertension, the acuteness of the problem, and the deoxygenation all suggest cardiac failure manifested as acute pulmonary edema in which the failing system is the cardiovascular with the respiratory system being only secondarily involved.

Flank pain may be generated from the gastrointestinal tract, the pelvic organs (reproductive), or the urinary system. The history of high calcium intake and the magnitude of the pain is most suggestive of ureteral stone, a common complication of excessive calcium intake in otherwise healthy individuals.

Acute diarrhea must be related to the gastrointestinal system, either as a primary infectious or inflammatory disorder or secondary to endocrine or systemic disease. The acuteness of the problem and its temporal relationship to a mountain camping trip are suggestive of an ingested organism, which has caused local bowel symptoms.

Amenorrhea in a healthy sexually active woman is pregnancy until proven otherwise. The primary system to be considered here is the reproductive, and the first tests are those for pregnancy. If pregnancy is disproven, then further consideration of less common causes for amenorrhea may be pursued.

**9. The answer is A.** careful detailed inspection should be the first component of every examination. The examination sequence for the abdominal examination differs from that of the chest or cardiac examination. Auscultation must come before palpation and percussion. Palpation and percussion may alter bowel sounds (i.e., decrease or increase their intensity). Auscultating first gives a more accurate representation of true bowel sounds.

**10. The answer is D.** Even normal spleens may be palpable in a thin patient. The technique of the examination is to have the patient take slow deep breaths and advancing fingers on expiration. The spleen becomes easier to palpate if the patient rolls to the right lateral decubitus position or places his or her left hand under the left buttock.

## The Kidney Examination

Genitourinary disorders may present nonspecifically but usually do so as abnormal clinical or laboratory manifestations suggesting a primary renal abnormality or a systemic disease associated with renal pathology. Normally, adults void about 4 to 6 times/day, mostly in the daytime, totaling 700 to 2000 mL/day.

### Symptoms and Signs

Asymptomatic patients with renal disease may have hypertension or abnormal blood or urine findings. They may have a family history of renal disorders (eg, polycystic disease, hereditary nephropathy). Routine antenatal ultrasonography may detect fetal renal abnormalities.

In symptomatic patients, fever, weight loss, and malaise are common findings with renal carcinoma, advanced renal failure, and urinary tract infections. Typically, renal symptoms include changes in nicturition, urinary output, or appearance; hematospermia in men; or pain, edema, and nonspecific symptoms and signs related to renal insufficiency.

**Frequent nicturition** without an increase in urine volume is a symptom of reduced bladder filling capacity. Infection, foreign bodies, calculi, or tumors may injure the bladder mucosa or underlying structures, leading to inflammatory infiltration and edema. Mild stretching of the bladder, reduced bladder elasticity, a pelvic mass, or a gravid uterus functionally reduces bladder capacity, resulting in pain and urgency (a compelling need to urinate). Incontinence may occur if voiding is not immediate. Urine volume is usually small, and the desire to urinate may be almost constant until the irritative process resolves.

**Polyuria** (> 2500 mL/day voided) may be caused by increased water intake (eg, compulsive water drinking), osmotic diuresis (eg, glycosuria from uncontrolled diabetes mellitus), decreased vasopressin release due to hypothalamic or posterior pituitary disease, or decreased renal tubular response to ADH from hypercalcemia, K deficiency, or congenital or acquired nephrogenic diabetes insipidus (NDI).

**Oliguria** (< 500 mL/day voided in adults or < 24 mL/kg body weight/day in young children) tends to be acute and caused by decreased renal perfusion (prerenal factors), ureteral or bladder outlet obstruction (postrenal factors), or primary renal disease. Uremia may occur.

**Anuria** (< 100 mL/day voided in adults), although rare, may signal acute renal failure, the end stage of chronic progressive renal insufficiency, or, rarely, renal infarction or cortical necrosis. It may also be due to reversible urinary obstruction. Prolonged anuria inevitably results in uremia.

**Nocturia** (voiding during the night) is an abnormal but nonspecific symptom. It may occur without disease; eg, due to excessive fluid intake in the late evening. It may result from urine retention secondary to bladder neck obstruction (eg, prostatism). Less commonly, nocturia may reflect early renal disease and polyuria from a decrease in concentrating capacity or heart and liver failure without evidence of intrinsic urinary system disease.

**Enuresis** (bed-wetting) is physiologic during the first 2 or 3 yr of life but later becomes an increasing problem. It may be caused by delayed neuromuscular maturation of the lower urinary tract or organic disease; eg, infection or distal urethral stenosis in girls, posterior urethral valves in boys, or neurogenic bladder in either sex.

**Dysuria** (painful urination) suggests irritation or inflammation in the bladder neck or urethra, usually due to bacterial infection. Persistent symptoms without such infection require careful evaluation of the bladder and urethra.

**Obstructive symptoms** (hesitancy, straining, decrease in force and caliber of the urinary stream, terminal dribbling) are commonly due to obstruction distal to the bladder. In men, such obstruction is usually due to prostatic obstruction or less often to urethral stricture or posterior urethral valves (which may be congenital in boys). Similar symptoms may suggest meatal stenosis in either sex.

**Urinary incontinence** (an uncontrollable loss of urine) may be caused by exstrophy of the bladder, epispadias, vesicovaginal fistula, ectopic ureteral orifices, congenital or acquired neurogenic (peripheral neuropathy, stroke, dementia) bladder dysfunction, or injuries due to prostatectomy or childbirth. In women, incontinence with mild physical stress (eg, coughing, laughing, running, lifting) is commonly due to urethral atrophy from a lack of estrogen or to a cystocele as a result of aging or stretching of the pelvic floor muscles during childbirth. Loss of urine due to bladder outlet obstruction or a flaccid bladder may produce overflow incontinence when the intravesicular pressure exceeds outlet resistance. Residual urine is always present with overflow incontinence.

**Pneumaturia** (the passage of gas in the urine) is rare. It usually indicates a fistula between the urinary tract and the bowel and may be a complication of diverticulitis, with abscess formation, enterocolitis, colon cancer, or vesicovaginal fistula. Rarely, pneumaturia may be due to gas formation from bacteriuria alone.

**Abnormal color** or appearance of urine has many causes. Urine may be clear during water diuresis or may be a deep yellow color when maximally concentrated due to chromogens (eg, urobilin). If excretion of food pigments (usually red urine) or drugs (brown, black, blue, green, or red) can be excluded, non-yellow urine suggests the presence of hematuria, hemoglobinuria, myoglobinuria, pyuria, porphyria, or melanoma. Cloudy urine is commonly due to precipitated amorphous phosphate salts in an alkaline urine; less frequently, it suggests pyuria due to a

UTI. Milky urine may be caused by precipitated phosphates in an alkaline urine. Brick dust urine usually is produced by precipitated urates in an acid urine. Urine microscopy and chemical analysis usually identify the cause.

**Hematuria** (blood in the urine) can produce red to brown discoloration depending on the amount of blood present and the acidity of the urine. Slight hematuria may cause no discoloration and may be detected only by microscopy or chemical analysis. Hematuria without pain usually is due to renal, vesical, or prostatic disease. In the absence of RBC casts (which usually indicate glomerulonephritis, silent hematuria may be caused by bladder or kidney tumor. Such tumors usually bleed intermittently, and complacency must not occur if the bleeding stops spontaneously. Intermittent, recurrent hematuria may also occur in IgA nephropathy. Other causes of asymptomatic hematuria include calculi, polycystic disease, renal cysts, sickle cell disease, hydronephrosis, and benign prostatic hyperplasia. Hematuria accompanied by excruciating pain (renal colic) suggests passage of a ureteral calculus or a clot from renal bleeding. Hematuria with dysuria is also associated with bladder infections or lithiasis.

**Kidney pain** usually is felt in the flank or back between the 12th rib and the iliac crest, with occasional radiation to the epigastrium. Stretching of the pain-sensitive renal capsule is the probable cause and may occur in any condition producing parenchymatous swelling (eg, acute glomerulonephritis, pyelonephritis, acute ureteral obstruction). There is often marked tenderness over the **kidney** in the costovertebral angle formed by the 12th rib and the lumbar spine. Inflammation or acute distention of the renal pelvis or ureter causes pain in the flank and hypochondrium, with radiation into the ipsilateral iliac fossa and often into the upper thigh, testicle, or labium. The pain is intermittent but does not completely remit between waves of colic. Chronic obstruction is usually asymptomatic.

**Bladder pain** is most commonly caused by bacterial cystitis; it is usually suprapubic and referred to the distal urethra during urination. Acute urinary retention causes agonizing pain, whereas chronic urinary retention due to bladder neck obstruction or neurogenic bladder usually causes little discomfort.

**Prostate pain** due to prostatitis may be felt as a vague discomfort or fullness in the perineal or rectal area, but prostatic disease is generally painless.

**Testicular pain** due to trauma or infection usually is severe.

**Edema** usually represents excessive extracellular water and Na due to abnormal renal excretion, but it may also be caused by heart or liver disease. Initially, edema may be evident only by weight gain but later becomes overt. Edema associated with **kidney** disease is sometimes noted first as facial puffiness rather than swelling in dependent or lower parts of the body. If fluid retention continues, anasarca (generalized edema) with fluid transudates (effusions) in the pleural and peritoneal

cavities may occur; it is most frequently associated with continuous, heavy proteinuria (nephrotic syndrome).

**Uremia** (a toxic condition associated with excessive accumulation in the blood of protein metabolism by-products) occurs when GFR declines to  $< 10\%$  of normal, with resultant disturbances of multiple organ systems. Weight loss, weakness, fatigue, dyspnea, anorexia, nausea and vomiting, itching, failure to grow, tetany, peripheral neuropathy, pericarditis, and convulsions are the usual symptoms and signs; most can be ameliorated or reversed by dialysis or renal transplantation and appropriate diet.

**Hypertension** may be secondary to renal disease (eg, vascular anomalies or occlusion, glomerulonephritis, progressive renal failure). However,  $\leq 5\%$  of adult hypertension is due to renovascular causes (with major renal artery or segmental artery obstruction and demonstrable increased renin secretion from the obstructed side).

**Skin changes** may include pallor, suggesting anemia, commonly associated with renal disease; excoriations, suggesting pruritus; and infections (eg, carbuncles, cellulitis), which may be due to glomerulonephritis. Skin lesions from vasculitis or endocarditis may suggest a possible cause of renal disease.

**Retinal abnormalities** on ophthalmoscopy may include hemorrhages, exudates, and papilledema as signs of cerebral edema associated with malignant hypertension or metabolic abnormalities.

**Other abnormalities** suggesting urinary system disease include stomatitis; an ammoniacal breath odor; and enlargement of the **kidneys**, bladder, or prostate on palpation.

## Laboratory Findings

**Blood studies: Hematologic assessment** may suggest renal disease. Anemia (particularly normocytic normochromic from a lack of erythropoietin) may be a clue to renal failure, but many other causes (eg, neoplasia, systemic inflammatory diseases) must be excluded. Polycythemia may occur in renal cell carcinoma or polycystic disease, but more common causes should be considered first.

**Serum chemistries** often are abnormal in renal dysfunction, but changes are nonspecific. For example, hypernatremia is most frequently due to lack of adequate water intake in an obtunded patient but can be produced by excessive water loss from a renal concentrating defect due to tubulointerstitial disease (eg, NDI, hypercalcemic or K depletion nephropathy). Serum  $\text{HCO}_3^-$  may be reduced by metabolic acidosis due to renal disease, by lactic acidosis, or by ketoacidosis. In

the absence of acute muscle damage, a persistent increase in serum creatinine is highly specific for renal dysfunction

**Urinalysis:** Urinalysis is the best guide to intrinsic GU disease and includes microscopic **examination** of sediment and qualitative evaluation of protein, glucose, ketones, blood, nitrites, and WBC esterase. Under standardized conditions, the solute concentration of urine (osmolality or sp gr) or urine pH may have diagnostic significance. Routine urinalysis in asymptomatic patients is infrequently positive and rarely leads to additional testing or changes in therapy. Only in pregnant women is there good reason to screen for bacteriuria (to prevent serious fetal and maternal sequelae) and proteinuria (to detect preeclampsia). However, routine urinalysis misses about 2% of patients with bacteriuria, and quantitative urine cultures are recommended instead. A useful and economic means of following women later in pregnancy after a negative culture may be repeat nitrite testing of first-morning voided specimens.

Particulate elements in urine, which can be separated and concentrated by forcing urine through a membrane filter, require special microscopy staining techniques but provide a permanent record. More commonly, 10 to 15 mL of freshly voided urine is centrifuged for 5 min at a slow speed (1500 rpm) and the supernatant decanted. The residue at the bottom of the centrifuge tube is best visualized in a special glass chamber of fixed volume, but an ordinary glass slide and coverslip will suffice. Using reduced light with the low-power objective, several fields are scanned. The light is increased and, with the high-power objective, specific cells and casts are identified. A semiquantitative estimation of these formed elements is made by a high-power or low-power field count (eg, 10 to 15 WBCs/high-power field).

Normal urine contains a few cells and other formed elements shed from the entire urinary tract. With disease, these cells are increased and may help localize the site and type of injury. Voided urine in women contains genital tract cells. Urinary system disease is suggested in a male by  $> 1$  WBC, RBC, or epithelial cell/high-power field (400 $\times$ ), ie,  $> 1000$  cells/mL, or in a female by  $> 4$  WBCs/high-power field, ie,  $> 4000$  cells/mL in centrifuged urine. Excessive WBCs may indicate infection or other inflammatory diseases. In symptomatic patients, the finding of  $> 10$  WBCs/ $\mu$ L strongly suggests significant bacteriuria. Occasional bacteria in a centrifuged urine sediment do not necessarily indicate UTI. However, bacteria in an uncentrifuged fresh urine sample together with urine cultures of  $> 10^5$  colony-forming units (CFU)/mL of voided urine suggest UTI rather than contamination.

Excessive RBCs may indicate infection, tumor, calculi, or inflammation anywhere in the **kidney** or urinary tract. When  $\geq 80\%$  of the RBCs are dysmorphic (wide range of morphologic variation), hematuria is likely to be glomerular in origin (see Ch. 224). In some clinical conditions, analysis of RBC morphology may be unreliable. For example, isomorphic erythrocyturia can be found in forced diuresis,

in glomerulonephritis with gross hematuria, or in renal insufficiency. A mixed morphologic pattern of urinary RBCs may occur in IgA nephritis, a frequent cause of glomerular hematuria. Recent identification of acanthocytes (ring-formed RBCs with one or more protrusions of different shapes and sizes) is a more specific marker of glomerular bleeding. Studies suggest that if 5% of the total urinary RBCs are acanthocytes, then an underlying glomerular disease can be diagnosed with high sensitivity (71%) and specificity (98%).

Crystals of various salts (eg, oxalate, phosphate, urate) or drugs (eg, sulfonamides) may be found when their concentrations and urinary pH exceed the limits of their solubility.

Casts (cylindric masses of mucoprotein in which cellular elements, protein, or fat droplets may be entrapped) in urine sediment are most important in distinguishing primary renal disease from diseases of the lower tract.

**Proteinuria** is simply and rapidly detectable by commercially available dipsticks. This technique is sensitive to as little as 5 to 20 mg/dL of albumin, the predominant protein in most renal diseases, but is less sensitive to globulins and mucoproteins and may be negative in the presence of Bence-Jones proteins. Electrophoresis, immunoelectrophoresis, and radioimmunoassays can also separate or quantitate various urinary proteins.

The major mechanisms producing proteinuria are elevated plasma concentrations of normal or abnormal proteins (overflow proteinuria; eg, lysozymuria in myelomonocytic leukemia, Bence-Jones proteinuria); increased tubular cell secretion (TammHorsfall proteinuria); decreased tubular resorption of normal filtered proteins; and an increase of filtered proteins caused by altered glomerular capillary permeability.

In adults, proteinuria is usually found incidentally during a routine physical **examination**. Proteinuria may be intermittent, orthostatic (occurring only when upright), or constant (persistent). Most patients with intermittent or orthostatic proteinuria do not show any deterioration of renal function, and in about 50% the proteinuria ceases after several years. Constant proteinuria is more serious. Although the course is indolent without other indicators of renal disease (eg, microscopic hematuria), most patients demonstrate proteinuria over many years; many develop an abnormal urine sediment and hypertension; and a few progress to renal failure.

Measurements of protein excretion are useful for diagnosis and follow-up, especially in constant proteinuria. A 24-h measurement of total protein excretion (normal, < 150 mg/day) may be done. Alternatively, in a random sample of urine, the protein:creatinine ratio (normally < 0.2) is measured. Heavy proteinuria (> 2 g/m<sup>2</sup>/day or a protein:creatinine ratio > 2) is found in patients with glomerulopathy producing the nephrotic syndrome (see Ch. 224).

Proteinuria usually is minimal, intermittent, or absent in diseases primarily involving the tubulointerstitial area (eg, pyelonephritis, analgesic nephropathy, benign nephrosclerosis, nephropathies of hypercalcemia and K depletion).

Exercise proteinuria sometimes occurs in joggers, marathon runners, and boxers. It is accompanied by elevation of catecholamines and may be associated with hemoglobinuria, hematuria, or even myoglobinuria.

For **glucosuria**, testing by dipstick is specific and very sensitive, detecting as little as 100 mg/dL (5.5 mmol/L) of glucose. The most common cause of glucosuria is diabetic hyperglycemia with normal renal glucose transport. However, if glucosuria persists with normal blood glucose concentrations, renal tubular dysfunction should be considered.

For **ketonuria**, the dipstick reagent is more sensitive to acetoacetic acid than to acetone and does not react with  $\beta$ -hydroxybutyric acid. Ketonuria usually is nonspecific, and acetoacetic acid, acetone, and  $\beta$ -hydroxybutyric acid are excreted in the urine. Finding any of these three compounds in urine generally is satisfactory for diagnosis of ketonuria. Ketonuria offers clues to the causes of metabolic acidosis. It is present in starvation, in uncontrolled diabetes mellitus, and occasionally in ethanol intoxication. It is not specific for intrinsic urinary system disease.

For **hematuria**, the dipstick reagent is sensitive to free Hb and myoglobin. A positive test in the absence of RBCs on microscopic examination suggests hemoglobinuria or myoglobinuria--an important etiologic clue in the patient with acute renal failure.

For **nitrituria**, the dipstick test depends on the conversion of nitrate (derived from dietary metabolites) to nitrite by the action of certain bacteria in the urine. Normally no detectable nitrite is present. When bacteriuria is significant, the test will be positive in 80% of cases in which the urine has incubated for  $\geq 4$  h in the bladder. Thus, a positive test is a reliable index of significant bacteriuria. However, a negative test does not exclude bacteriuria. Reasons for a negative test in the presence of bacteriuria include insufficient bladder incubation time for conversion of nitrate to nitrite, low urinary excretion of nitrate, absence in some urinary pathogens of the enzymes to convert nitrate to nitrite, and reduction of nitrates to nitrogen by bacterial enzymes.

**WBC esterase** is found in azurophilic or primary neutrophil granules. Its detection, indicating the presence of WBCs, is a surrogate for bacteriuria, but it actually suggests the presence of inflammation from any source, bacterial infection being the most common. False-negative results may occur in the presence of very concentrated urine, glycosuria, urobilinogen, phenazopyridine, nitrofurantoin, rifampin, and large amounts of vitamin C.

**Osmolality** is the total concentration of solutes in urine, expressed as mOsm/kg (mmol/kg) of urine water. It is best determined by an osmometer. Normal urine osmolality is 50 to 1200 mOsm/kg depending on the circulating titer of vasopressin and the rate of urinary solute excretion. Although loss of urinary concentrating capacity is a sensitive test of renal dysfunction, measurement of urine osmolality (or sp gr) in a randomly voided urine sample is only helpful when it is > 700 mOsm/kg (sp gr > 1.020), which excludes significant tubulointerstitial disease. Lower osmolality values may be normal or abnormal depending on the prior state of hydration.

**Urinary sp gr** is measured by a urinometer or estimated by refractive index (refractometer) or a sp gr reagent strip method. Although the correlation with osmolality is not linear, it is satisfactory for clinical use, except when large amounts of glucose or high mol wt solutes such as protein or organic iodides (radiocontrast agents) are present. Unlike the urinometer and refractometer, which give abnormally high values in contrast to the lower osmolality values, the sp gr reagent strip does not require correction for the presence of these compounds.

**Urinary pH** is measured by a dipstick impregnated with various dyes that change color when the pH is 5 to 9. Although this test is done routinely, it does not identify or exclude patients with urinary system disease. However, it often helps identify various crystals that may be found in urine on microscopy. Testing of urine with a pH meter is critical in diagnosing the distal type of renal tubular acidosis, which is suggested by a urine pH > 5.5 after an acid load. The urinary pH in patients with other types of renal disease usually varies relatively normally, although the capacity to excrete titratable acid and ammonia may be reduced.

**Quantitative urine cultures:** A **culture sample** that reflects bladder urine must be obtained without undue contamination from other sources. This can be achieved directly by urethral catheter or suprapubic needle aspiration of the bladder. Noninvasive techniques using clean midstream-voided urine collection and quantitative culture methods usually give adequate information without the hazards of instrumentation. Interpretation of urinary CFU levels must consider the patient's clinical presentation.

**Localization studies** are based on the hypothesis that bacteria coming from the ureters suggest renal infection. Most patients with UTI have bladder bacteriuria without evidence of tissue invasion, which readily responds to appropriate antimicrobial treatment (unless there is urinary tract obstruction); localization studies are not indicated. However, for a patient with frequent relapsing infections, localization studies may help uncover the cause and lead to different therapy. The bladder washout method is probably the most benign localization procedure, because it avoids cystoscopy and ureteral catheterization.

**Measurement of renal function:** Renal function tests (see [Table 214-5](#)) are useful in evaluating the severity of **kidney** disease and in following its progress.

**Serum creatinine** can be used as an index of renal function because creatinine production and excretion are reasonably constant in the absence of muscle disease. Serum concentration of creatinine varies inversely with the GFR and therefore is a useful index of the GFR if production (related to muscle mass and age) and metabolism (increased in uremia) are considered. The upper limit of serum creatinine concentration in men with normal GFR is 1.2 mg/dL (110  $\mu$ mol/L); in women, 1 mg/dL (90  $\mu$ mol/L).

**Creatinine clearance** in men is 140 to 200 L/day ( $70 \pm 14$  mL/min/m<sup>2</sup>) and in women, 120 to 180 L/day ( $60 \pm 10$  mL/min/m<sup>2</sup>). The creatinine clearance ( $Cl_{\text{creat}}$ ) can be calculated from the serum creatinine concentration in men as:

$$Cl_{\text{creat}} \text{ (mL/min)} = \frac{(140 - \text{age [yr]})(\text{body wt [kg]})}{(72) (\text{serum creatinine [mg/dL]})}$$

In women, the calculated values are multiplied by 0.85.

Creatinine clearance is not useful for detecting early **kidney** damage due to hypertrophy of residual glomeruli. After loss of 50 to 75% of the normal glomerular filtration surface, a decrease in creatinine clearance is clearly detectable. Thus, a normal creatinine clearance cannot exclude the presence of mild renal disease.

**BUN**, in contrast to serum creatinine, is unsuitable as a single measure of renal function because it is influenced by variations in urine flow rate and by the production and metabolism of urea. The BUN:creatinine ratio often is used to differentiate prerenal, renal, or postrenal (obstructive) azotemia. A ratio > 15 is abnormal and suggests prerenal or postrenal azotemia. The BUN:creatinine ratio also is elevated whenever urea production is increased by diet, TPN, or glucocorticoid therapy; with some neoplasms and antibiotics; and with excessive protein catabolism, as seen in infections and uncontrolled diabetes mellitus. Common causes of prerenal azotemia include shock, ECF depletion, massive GI hemorrhage, severe heart and liver failure, and bilateral tight renal artery stenosis. The BUN:creatinine ratio is normal in renal azotemia. The ratio is low in pregnancy, overhydration, severe liver disease, and malnutrition.

Tests of **renal concentrating capacity** are simple and diagnostically helpful. A loss of concentrating capacity in the presence of adequate vasopressin stimulation is associated with tubulointerstitial disease (edema, infiltrate, fibrosis), except when NDI is present. The loss of concentrating ability frequently is present long before a depression of GFR is measurable. Renal concentrating capacity is best tested by water deprivation for 12 to 14 h and by the response to exogenous vasopressin. After the patient has fasted for 12 to 14 h overnight, the osmolality of

the initial morning urine and of subsequent hourly samples is measured. When hourly measurements differ  $< 30$  mOsm/kg or sp gr  $< 0.001$ , the maximum concentrating capacity has been reached with water deprivation. Aqueous vasopressin 5 U sc or desmopressin 10  $\mu$ g by nasal insufflation is given, and the urine osmolality is measured after another hour. (**Caution:** *In patients with renal failure, water deprivation may be harmful and usually is not useful in diagnosis; the concentrating capacity is always abnormal when the GFR is significantly reduced.*) A lack of response to water deprivation or exogenous vasopressin suggests an intrinsic renal concentrating defect that may be due to one or more of the following functional tubular impairments: congenital (eg, NDI, Fanconi's syndrome) or acquired (eg, osmotic diuresis, certain diuretics [furosemide, bumetanide, ethacrynic acid], K deficiency, hypercalcemia). Otherwise, tubulointerstitial disease should be considered, as in sickle cell disease, toxic nephritis, pyelonephritis, or any renal disease severe enough to produce azotemia. For other responses to these tests and their interpretations.

Measurement of the **renal plasma flow** is no more useful clinically than the GFR but is more difficult and costly.

Additional **special tests** of renal tubular function usually require research laboratories and are reserved for patients with specific problems. However, tests that measure plasma phosphate and urate, urinary amino acids, and urine pH are readily available and may prove useful in screening specific clinical problems.

**Imaging procedures: Plain x-ray of the abdomen** (kidney, ureter, bladder [KUB] film) can demonstrate the size and location of the kidneys but has been superseded by ultrasonography (US). Because GI and GU diseases tend to mimic each other, KUB film may be helpful in the differential diagnosis. However, the renal outline can be obscured by bowel content, lack of perinephric fat, or a perinephric hematoma or abscess. This difficulty may be overcome by CT. Congenital absence of a kidney may be suggested. If both kidneys are unusually large, polycystic kidney disease, multiple myeloma, lymphoma, amyloid disease, or hydronephrosis may be present. If both are small, the end stage of bilateral renal dysplasia or sclerosing disease (eg, glomerulonephritis, tubulointerstitial nephritis, nephroangiosclerosis) must be considered. Unilateral enlargement suggests renal tumor, cyst, or hydronephrosis, whereas a small kidney on one side is compatible with congenital dysplasia, atrophic pyelonephritis, or an ischemic kidney. Normally, the left kidney is 0.5 cm longer than the right.

In 90% of cases, the right kidney is lower than the left because of displacement by the liver. The long axes of the kidneys are oblique to the spine and tend to parallel the borders of the psoas muscles. If both kidneys are parallel to the spine, the possibility of horseshoe kidneys should be considered. If only one kidney is displaced, a tumor or cyst may be present.

Because x-ray film is two-dimensional, a calculus in the urinary tract is practically impossible to diagnose unless it is a staghorn calculus. However, suspicious opaque bodies may be noted in the region of the adrenal, kidney, ureter, bladder, or prostate. Oblique and lateral films and visualization of the urinary tract with radiocontrast agents, US, or CT are necessary to place the calcification specifically within these organs.

**Intravenous urography** (IVU; excretory urography; commonly but incorrectly referred to as intravenous pyelography) is often used to visualize the kidney and lower urinary tract. Studies are done by IV infusion of an iodinated benzoic acid derivative. The iodine provides radiopacity, while the benzoic acid is rapidly filtered by the kidney. A contrast agent, after IV injection, becomes concentrated in the renal tubules in  $\leq 5$  min, providing a nephrogram. Renal CT is often performed routinely at this stage to show renal outlines that may otherwise be obscured by overlying gas or bowel content. In addition, cysts frequently can be differentiated from solid neoplasms. Later, the contrast agent appears in the collecting system, outlining the renal pelvis, the ureters, and finally the bladder. Visualization depends on the concentration of the contrast agent in the kidneys and the urinary collecting system. Therefore, the best radiograms are obtained in patients with a normal GFR who do not actively diurese during contrast agent administration. An adequate study in patients with BUN  $> 50$  mg/dL ( $> 17.8$  mmol urea/L) or plasma creatinine  $> 3$  mg/dL ( $> 270$   $\mu$ mol/L) usually is difficult. For azotemic patients, another renal imaging technique (eg, US, CT if indicated) is less risky and is preferred.

IVU is indicated when investigating causes for recurrent UTI or when the site of obstruction produces hydronephrosis, vesicoureteral reflux, hypertension, and urolithiasis. If renal injury is suspected, IVU will confirm that the uninjured kidney is normal and will provide functional information about the injured kidney. However, in urinary system trauma, CT (or sometimes angiography) is preferred.

**(Caution:** *Acute renal failure occasionally occurs [incidence  $< 0.5\%$ ] after radiocontrast procedures in low-risk patients. The mechanism is unknown, but concomitant risk factors for contrast-associated nephropathy include prior renal insufficiency, diabetes mellitus, advanced age, extracellular volume depletion, and multiple myeloma. When contrast studies are done in high-risk patients, adequate extracellular volume expansion, nonionic contrast, and a reduced contrast dose may reduce the risk.*)

In **retrograde pyelography**, radiopaque agents similar to those used in IVU are introduced directly into the urinary tract after cystoscopy and catheterization of the ureter. Retrograde pyelography provides more intense opacification of the collecting and voiding system when IVU has been unsuccessful because of poor renal function, a nonvisualized kidney by IVU, upper urinary tract bleeding with normal IVU, or filling defect in the upper urinary tract. Additionally, retrograde

evaluation may be indicated to assess the degree, type, cause, and length of ureteral obstruction or when the patient is allergic to IV radiocontrast. It is also useful for detailed **examination** of the pelvicalyceal collecting system, ureters (including suspected ureterovaginal fistula), and urinary bladder. Disadvantages are potential infection, distortion of the calyces by overdistention, backflow phenomena that obscure detail, acute ureteral edema and secondary stricture formation, and the need for anesthesia.

In **anterograde pyelography**, radiocontrast agents are introduced into the renal pelvis by radiographic visualization. This procedure may be indicated when retrograde pyelography cannot be done because of inability to catheterize a ureter, severe bladder disease, ectopic or reimplanted ureter, or inability to inject radiocontrast above an obstructed site in a ureter.

**CT** is more expensive than US and IVU. However, CT is most useful in evaluating the character and extent of renal masses or determining the cause of a retroperitoneal mass distorting the normal urinary tract (eg, an enlarged abdominal lymph node). Renal cysts are of low density on CT. After IV injection of radiocontrast, there is no enhancement; the cyst stands out as a prominent lucency against the contrast-containing parenchyma. Renal carcinoma, conversely, generally is isodense on the unenhanced scan and, after administration of IV radiocontrast, shows an increased density due to hypervascularity of the lesion. Contrast enhancement often helps demonstrate necrotic areas within the mass and areas of fat content that suggest angiomyolipoma. The extent of extrarenal involvement by a tumor often can be determined. When bladder carcinoma is suspected or known, CT with sequential intravesical air and radiocontrast is also useful.

**Angiography** is the most invasive renal imaging procedure and is reserved for special indications. Contrast agents can be introduced by the retrograde method, in which a catheter is inserted through a peripheral artery (femoral, axillary) and extended to the desired area in the aortic lumen, and by the translumbar method, now rarely used, in which percutaneous needle puncture of the aorta is performed.

**Ultrasonography (US)**, a noninvasive, relatively innocuous technique, is advantageous in that visualization does not depend on function. Nevertheless, some functional information can be inferred, especially in the fetus, in whom the **kidneys** can be identified after about 20 wk gestation, permitting measurement of urine production rate by serial estimations of the bladder volume. For neonates, US is the first choice for investigating abdominal masses, UTI, and suspected anomalies of the urinary system because it is atraumatic and yields highly accurate results.

**MRI** offers information about renal masses that cannot be determined by other techniques. It allows direct imaging in the transverse, coronal, and sagittal planes.

Morphologic data are obtained from three-dimensional reconstruction of the tissue. Solid and cystic renal lesions are as readily distinguished by CT, but MRI provides information about the cyst fluid to help differentiate hemorrhage and infection. In addition, MRI defines vascular and perirenal structures, permitting diagnosis of thrombosis, aneurysm, arteriovenous fistula, and neoplastic extension. In the pelvis, MRI shows tissue planes and can demonstrate the seminal vesicles and the extent of wall invasion by bladder cancer. MRI is limited by respiratory motion and peristalsis. Intrarenal calcifications are poorly defined because they have few mobile protons.

MRI with contrast using gadolinium pentetic acid administered by bolus injection and rapid sequence imaging is increasingly used. This technique provides information about GFR and tubular function.

**Morphologic procedures: Renal biopsy** is performed to establish a histologic diagnosis, help estimate prognosis and the potential reversibility or progression of the renal lesion, estimate the value of therapeutic modalities, and determine the natural history of renal diseases. The only absolute contraindication to biopsy is uncontrollable bleeding. Biopsy of a solitary native kidney is a relative contraindication to be weighed against the need for information. Biopsies of a single, functioning, transplanted kidney are done frequently to evaluate various types of nephropathy (eg, graft rejection, drug toxicity, recurrence of primary renal disease). Conditions associated with increased morbidity after biopsy are deemed relative contraindications: eg, renal tumors, large renal cysts, hydronephrosis, perinephric abscesses, severe reduction in blood or plasma volume, severe hypertension, and advanced renal failure with symptoms of uremia.

Open biopsy is rarely necessary--only when the percutaneous method has been unsuccessful or when direct visual control of the biopsy is critical. For the percutaneous technique the patient is sedated, and the kidney is visualized by radiography or US. With the patient in the prone position, after the overlying skin and muscles of the back are anesthetized, the biopsy needle is inserted and tissue is obtained for light, electron, and immunofluorescent microscopy.

**Urine cytology** is useful in screening for possible urinary tract neoplasia in high-risk populations (eg, petrochemical workers, patients with painless hematuria from nonrenal causes) and in following patients after resection of bladder tumors. The initial and several consecutive voidings are examined for abnormal exfoliated cells. Cytology is abnormal in 70 to 85% of patients with known urinary tract epithelial neoplasia, but inflammatory or reactive hyperplastic lesions of the urinary tract or cytotoxic drugs for nonurogenital carcinoma may produce false-positive results. In asymptomatic patients, the incidence of carcinoma cells in the urine is about 0.1%. False-negative findings usually are associated with neoplasia that appears low-grade on histology. Diagnostic accuracy may be increased for bladder neoplasms by vigorous bladder lavage with a small volume of 0.9% NaCl solution (50 mL

pushed in and then aspirated by syringe through a catheter). The cells collected in the saline are concentrated and examined.

Diseases of the kidneys and urinary tract frequently give rise to consistent arrays of **clusters of clinical signs, symptoms, and laboratory findings called syndromes**. Syndromes are useful diagnostically because each has fewer causes than the individual clinical signs and it contains.

**TABLE 1. Initial clinical and laboratory data base for defining major syndromes in nephrology**

| Syndromes                 | Important clues to diagnosis  | Findings which are common but not of                    |
|---------------------------|---|---|
| Acute renal failure       | Anuria<br>Oliguria Documented recent decline in GFR   | Hypertension, Proteinuria, hematuria                    |
| Acute nephritis           | Hematuria. RBC casts  | Casts, edema<br>Proteinuria                             |
| Chronic renal failure     | Azotemia, oliguria<br>Edema, hypertension<br>Azotemia for > 3 months  | Pyuria<br>Circulatory congestion                        |
| Nephrotic syndrome        | Prolonged symptoms or signs of uremia<br>Symptoms or signs of renal osteodystrophy<br>Hypoalbuminemia<br>Hyperlipidemia   | Hematuria, proteinuria<br>Casts, oliguria<br>Edema      |
| Urinary tract infection   | Bacteriuria > 10 <sup>5</sup> colonies per milliliter<br>Other infectious agent documented in urine<br>Pyuria, leukocyte casts<br>Frequency, urgency <sup>o</sup><br>Polyuria, nocturia | Hematuria<br>Mild azotemia<br>Mild proteinuria<br>Fever |
| Hypertension              | Symptoms or signs of renal osteodystrophy   | Hematuria<br>"Tubular" proteinuria<br>Enuresis<br>Casts |
| Nephrolithiasis           | Previous history of stone passage or removal  | Azotemia<br>Hematuria                                   |
| Urinary tract obstruction | Previous history of stone seen by x-ray<br>Renal colic<br>Azotemia, oliguria, anuria  | Pyuria<br>Frequency, urgency                            |

### Study questions

- 1. Normal adults excrete proteins:**
  - A. Less than 150 mg/24-hour period**
  - B. Less than 1 mg/24-hour period**
  - C. More than 150 mg/ 24-hour period**
  - D. More than 500 mg/ 24-hour period**
  
- 2. Normal urine usually contains only one from following components detectable with commercially available dipsticks :**
  - A. Blood**
  - B. Glucose**
  - C. Ketonic bodies**
  - D. Proteins**
  - E. Bilirubin**
  
- 3. Urinary sediment from normal urine preparing by centrifugation contains only one from following components:**
  - A. Bacteria**
  - B. Erythrocytes**
  - C. More than 1-3 leukocytes**
  - D. Casts**
  
- 4. Urine output less than 100 ml/day is:**
  - A. Oliguria**
  - B. Polyuria**
  - C. Nocturia**
  - D. Anuria**

### **Questions 5-8**

**For each of the case scenarios presented below, choose the most likely body system implicated.**

- (A) Musculoskeletal**
- (B) Renal-urinary**
- (C) Respiratory**
- (D) Reproductive**
- (E) Gastrointestinal**

5. A 23-year-old runner comes to the outpatient department with a complaint of persistent pain in the left knee and calf since Sunday's marathon.
  
6. A 72-year-old hypertensive man comes into the emergency room with acute shortness of breath, cyanosis, and rales throughout both lung fields.
  
7. A 32-year-old woman who has been taking high doses of calcium to prevent

osteoporosis comes in with a 2-hour history of excruciating left flank pain.

8. A 25-year-old man comes to the clinic with a 3-day history of 10-12 loose stools a day, which began while he was camping in the Rocky Mountains.

**And of group**

**question**

**9. Acute renal failure is accompanied with all phenomena besides one:**

- A. Anuria
- B. Serum urea more than 8 mMol/l
- C. Glomerular filtration rate less than 50 ml/min.
- D. Serum creatinine more than 120 mcMol/l

**10. Diseases of the kidney are accompanied with all phenomena besides one:**

- A. Hypertension
- B. Proteinuria
- C. Cough
- D. Erythrocyturia
- E. Leukocyturia

### Answers and explanations

1. **The answer is “A”** Protein usually is not present in normal urine above 150 mg/day. Proteinuria about 500 mg/day indicates kidney damage.

2. **The answer is “C”** Ketonic bodies are present in the urine of healthy individuals during fasting. Blood, Proteins, Bilirubin detectable with commercial dipsticks are not present in urine of healthy persons.

3. **The answer is “A”** Bacteria are present in small quantities in normal urine sediments. Erythrocytes, Leukocytes (more than 1-3), Casts - are not.

4. **The answer is “D”** Urine output less than 100 ml/day is Anuria. Oliguria –urine output less than 500 ml/day. Polyuria is more than 2l urine a day. Nocturia – more urine at night than per day.

**5-8. The answers are: 5-A, 6-E, 7-B, 8-E.** Young adult~, are commonly seen for traumatic injuries to the muscles and joints, especially those individuals who are strenuously physically active. The temporal relationship to the marathon should alert the clinician to the high probability of a musculoskeletal problem.

Despite the fact that this 72-year-old man presents with what appear to be respiratory problems, the history of hypertension, the acuteness of the problem, and the deoxygenation all suggest cardiac failure manifested as acute pulmonary edema in which the failing system is the cardiovascular with the respiratory system being only secondarily involved.

Flank pain may be generated from the gastrointestinal tract, the pelvic organs (reproductive), or the urinary system. The history of high calcium intake and the magnitude of the pain is most suggestive of ureteral stone, a common complication of excessive calcium intake in otherwise healthy individuals.

Acute diarrhea must be related to the kidney, either as a primary infectious or inflammatory disorder or secondary to endocrine or systemic disease. The acuteness of the problem and its temporal relationship to a mountain camping trip are suggestive of an ingested organism, which has caused local bowel symptoms.

Amenorrhea in a healthy sexually active woman is pregnancy until proven otherwise. The primary system to be considered here is the reproductive, and the first tests are those for pregnancy. If pregnancy is disproved, then further consideration of less common causes for amenorrhea may be pursued.

9. **The answer is “C”** Glomerular filtration rate more than 115 ml/min. Anuria is main sign of the acute renal failure. Serum urea more than 8 mMol/l, Serum creatinine more than 120 mMol/ are signs of the asotemia by the acute renal failure.

10. **The answer is “C”** Cough is sign of lung diseases. Hypertension, Proteinuria, Erythrocyturia, Leukocyturia – all are symptom's of the kidney diseases.

6

## **Approach to patients with endocrine gland and metabolism disorders**

### **METHODS OF CLINICAL RESEARCH**

**Complaints.** Because of regulator role of the endocrine system in the basic processes of vital functions, pathology of most endocrine organs is accompanied by various clinical symptoms which have the complaints of general character. Prevalent are often weakness, rapid fatigue ability, bad feeling, low-spirited or excitative mood, decline and/or loss of capacity, head pain, bad or promoted appetite and others like that. It is sometimes heavy to understand, of what organ such complaints testify. Therefore it is important to estimate not alone or a few pathological symptoms, but all clinical symptoms of disease – cold syndromes (see below).

**History of Present Illness, and Past Medical History.** Questioning a patient, the special attention needs to be paid to his mental development, adequacy of conduction, heredity which it is is often burdened. Quite often it is possible to expose the direct reason of disease – psychical or physical trauma, sharp infectious disease, influencing of professional factors (toxic matters of a different origin) and others like that. Quite often many diseases arise up on a background obesity (diabetes mellitus, myxedema, pathology of diencephalic area of brain).

### **OBJECTIVE INSPECTION**

**Inspection.** The extraordinarily large value for diagnostics of endocrine diseases has the inspection of patient. It is often already the first look of doctor on a patient enables to suspect or even recognize such diseases, as diffuse toxic goiter, mixedema, acromegalia, gigantism, hypophysis dystrophy, nanism, the Addison disease.

In future attention on growth of body, sizes, form and correlation of separate his parts, lines of person and form of skull applies in the case of review of patient.

Giant growth or *gigantism* (growth over 195 sm at women and 200 sm at men) is mostly conditioned by hyperfunction of front lobe of the hypophysis. Nanism - growth *less than 135 sm can be with proportional parts of body, as at the grown man, or disproportionate, as at a child. Normal growth in combination with the disproportionate increase of distal parts of body (carried, lips, chins, brushes of hands, foot) is the certificate about hyperfunction of front lobe of the hypophysis.. More frequent l it is in the case of adenoma (tumor) of front lobe to the hypophysis – acromegalia. Symptoms which appear by dentists are the characteristic signs of this disease is considerable increase of lower jaw and divergence of teeth*

(*diasthema*), *increase of tongue* The changes of thorax are characteristic. A wide, short thorax is in the case of the Icenko-Cushing disease, and wide and high – in the case of acromegalia.

It is the changes of patient well-fedding – obesity or growing thin up to exhaustion are often in the case of endocrine pathology marked (*cachexy*). At a patient with obesity the special attention it is necessary to spare to the features of distributing on the body of hypodermic fat, which depend on character of endocrine pathology..

In the case of increase of function of cora of adrenal glands (hypercorticism), that is at disease or the Icenko-Cushing syndrome, there is the special type of obesity which named *Cushingoid*.

The considerable and rapid loss of weight is marked in the case of diffuse toxic goiter, diabetes mellitus and the Simmonds disease (*hypophysis cachexy* which women are mostly ill by age 20-40 years). At patients with endocrine pathology more frequent is the origin of cramps in the case of hypoparathyrosis, especially after operations on a thyroid gland.

The large value patient research is description of skin, hair cover and nails. Dry, fragile hairs, fall of him on a head, in the area of external parts eyebrow, in arm-pits pits it is often are the displays of hypothyroidism. The cases of darkening of hairs, moderate fall of him, in arm-pits pits are the certificate of chronic insufficiency of cortex of adrenal glands.. Growth of hairs masculine type at women (surplus growth of hairs on feet, trunk, face and fall of him on a head) is in the case of the Icenko-Cushing disease, corticosteroma, androsteroma.

Total bronze (hazel) color of skin, with strengthening of pigmentation quite often in combination with pigmentation of mucus shell of mouth cavity is the symptom of chronic insufficiency of cora of adrenal glands are the Addison diseases.

Noticeable pigmentation of elbows, neck and other areas of skin is observed in the case of the Icenko-Cushing disease, and easy pigmentation of skin, it is more frequent round eyes – in the case of diffuse toxic goitre.

Opposite, cold, dry, wrinkled, pale, dense, thickened, senile kind a skin is the characteristic sign of гіпотиреозу. Quite often the edemata of надключичних areas, external surface of brushes, shins appear on a background this pathology (pretibial myxedema). After pressure there is absence of pit on such skin. Endocrine pathology it is often shows up the changes on face of patient. In the case of гіпотиреозу weak mimicry or complete its absence, narrowing of eyeing cracks on a background a filling skin out is marked.

**Palpation.** By palpation it is possible to explore thyreoid and sexual glands. Their size, closeness, evenness or unevenness of consistency (knotted) is thus determined, pains and others like that.

*Palpation can be executed by two methods – front (a doctor stands before a patient and back (a doctor stands behind a patient).*

**Percussion.** This method for research of ductless glands has the limited value. By percussion it is possible to expose a goiter which is placed after brestbone. During pattering by a percussion hammer below temple sprout

**cramps of muscles of corner of mouth, porches of nose (the Chvostec symptom) can be caused, that testifies to the promoted neuromuscular excitability in the case of hypoparathyreosis.**

**Auscultation.** In endocrinology auscultation finds itself only one application for research of mega thyroid gland behind breastbone, when it is possible to hear systolic murmur which arises up in its extended arterial vessels.

## **LABORATORY AND FUNCTIONAL RESEARCH**

### **LABORATORY DIAGNOSTICS**

#### **DETERMINATION OF LEVEL OF HORMONES IN BLOOD**

*The methods of radioimmune analysis (RIA)* are most exact and informing for determination of concentration of hormones in a blood. They do not need introduction to the patient to the radioisotope, and is executed *in vitro* with the use of radioimmune sets which contain hormones with the marked radio-active atoms.

**Hormones of hypophysis.** In a norm maintenance of corticotropine (ACTH) in plasma of blood in the morning on empty a stomach hesitates within the limits of 10-80 нг/л (or 0-33,0 пмоль/л after the International system of units), thyrotropine (TTH) – 1-3 мкг/л (or 0,23-4 мОД/л). Increases of maintenance of growth (somatotropine) hormone are observed in the case of acromegalia, gigantism, and decline – at presence of nanism. In a norm maintenance of this hormone in a blood hesitates from 0,3 to 6,5 мкг/л (or 0-264 пмоль/л at men and 0-440 пмоль/л at women after the International system of units).

For diagnostics of undiabetes mellitus maintenance of hormone of neurohypophysis vasopressine is determined in a blood and urine.

**Hormones of thyroid gland.** By the RIA Method is determined: general thyroxine – GT4, free thyroxine – FT4, triiodothyronine – T3..

From data of RIA inspection, concentration of GT4 in the blood at healthy persons makes 51,5-141,6 nmol/l, FT4 – 11,8-24,6 pmol/l. For determination of concentration of general T3 with application of specific antibody to T3. Concentration of him in the whey of blood more low from the level of T4 and makes 1,54-3,85 pmol/l.

**Hormones of pancreas.** By a RIA method maintenance is determined in the blood of immunoreactive insulin (IRI) and glucagone. On the average the IRI maintenance in plasma of blood on empty stomach at healthy people makes 128 pmol/l (86-180 pmol/l).

In practical medicine for diagnostics of diabetes mellitus considerably more simple methods of determination of glucose in a blood and urine are used.

### **LABORATORY RESEARCH IN THE CASE OF DIABETES MELLITUS**

For estimation of the functional state of islets of pancreas maintenance of glucose is determined in a blood on empty stomach and for a day long (glycemic profile). Laboratory methods which determine restoration properties of glucose

(the Chagedorn-Iensen method) or its colour reactions with certain reagents are applied (a orthotoluidine method). The last method is more precisely, because does not determine maintenance of all restoration matters in a blood, only glucose. In a recent year got distribution of determination of glucose by automatic analyzers. More frequent all the maintenance of glucose is determined in a capillary blood.

At healthy people on (through 8-12 h after the last reception of meal) empty stomach at complete physical and psychical rest maintenance of glucose in a blood hesitates in scopes from 3,33 to 5,55 mmol/l, and for a day long – from 4 to 8-9 mmol/l depending on the feed and functional state of organism.

The diagnosis of diabetes mellitus is set, if determine *glycemia* on empty a stomach 6,1 mmol/l and anymore or by chance among days more high 11 mmol/l. For confirmation of results the analyses must be repeated 2-3 times per other days. At patients with diabetes mellitus a glycemic type – determination of level of glucose of blood is explored also through each 3 h.

For diagnostics of the hidden diabetes mellitus *a пероральный test* is used *on tolerance to glucose* (glucosae-tolerans test).

Maintenance of glucose is determined in a blood on (through 10-14 h after the last use of meal) empty a stomach, and also through 1 and 2 h after the use of a 75 g dry matter of the glucose dissolved in 250-300 ml water, during 2-5 min. During conducting of test a patient is forbidden to execute some physical loadings.

At healthy people after loading by glucose глікемії usually reach level a maximum through 30-60 min, then gradually goes down to the initial size during 2 h.

Pursuant to the criteria of Committee of experts WHO on the questions of diabetes mellitus (1981), presence of glycemia through 2 h after the per mouth loading by glucose below than 8 mmol/l is considered normal, within the limits of 8-11 mmol/l – testifies to violation of tolerance to the carbohydrates, and 11 mmol/l and higher – is the sign of diabetes mellitus.

In urine of healthy people glucose is absent, as fully reabsorbt in kidney. Glucose appears in urine, when the level of her in a blood exceeds the capacity of buds for rheabsorbchen ( threshold – 8,88-9,99 mmol/l). The positive reaction of urine on glucose (glucosurea) *is the sign of diabetes mellitus, but can be also observed at the use of plenty of sugar, in the case of pregnancy, tumours of brain, epilepsy, meningitis and others like that.*

Determination of acetone in urine is used for diagnostics of the ketoacidotic states in the case of decompensation of diabetes mellitus by the set for diagnostics of acetone at urine, with indicator strips.

## LABORATORY RESEARCH IN THE CASE OF VIOLATIONS PHOSPHORIC-CALCIUM EXCHANGE

The function of parathyroid glands can be estimated on the indexes of calcium-phosphoric exchange. The level of calcium of whey of blood in a norm is 2,25-2,75mmol/l. In the case of hypoparathyrosis in a blood is multiplied maintenance of general and ionized calcium (especially in the case of bone forms of defeat).

The table of contents of inorganic phosphorus in a blood in a norm makes 0,65-1,29 mmol/l. For hypoparathyrosis characteristic is hyperphosphatemia.

## **LABORATORY RESEARCH IN THE CASE OF PATHOLOGY OF ADRENAL GLANDS**

After a RIA method in the blood of healthy people maintenance of free 17-OKS makes 16,4-32,8 nmol/l, and with urine during time of 24 h from 7,23 to 15,43 mmol/l.

After a phluorometric method maintenance in the blood of total 11-OKS in a norm makes 140-230 mkg/l.

## **FUNCTIONAL RESEARCHES OF THYREOID GLAND**

For research structures and functions of thyreoid gland are widely used RADIONUCLIDE and ultrasonic methods which objective enough and informing.

## **РАДІОНУКЛІДНІ METHODS OF RESEARCH OF THYREOID GLAND**

In clinical practice for diagnostics of diseases and defeats of thyreoid gland of most distribution such functional methods were acquired:

- gamma-thopographic method is RN scanning or scintygraphy of thyreoid gland;

Scintygraphy also effective for estimation of the state after operations on a thyreoid gland, in the case of relapse of thyreotoxicosis, cysts and others like that.

## **ULTRASONIC RESEARCH OF THYREOID GLAND**

A thyreoid gland has a relatively simple echo structure. The review of it by ultrasonic methods is possible it is always, except for the change of structure of surrounding tissues (deformations of neck, scars of skin) or behind bresbone location of gland. This method takes, no doubt, advantage due to informing and simplicity of application.

## **ROENTGENOLOGIC RESEARCHES IN ENDOCRINOLOGY**

*On the surveying x-Ray's of skull the direct and mediated signs of tumor defeat of hypophysis are exposed. Calcinosis of tumor belong to the lines. The indirect are included at itself: changes of bones of basis of skull, vessels, cavities of brain, related to growth of tumor, above all things deformation of the Turkish saddle.*

The thyreoid gland placed behind brestbone shows up on x-Ray's additional shade in top midsternum. The increase of thyreoid gland mediated shows up displacement and deformation of gullet and trachea (narrowing of road clearance, increase of distance between them).

## COMPUTER TOMOGRAPHY

By computer tomography it is possible in detail layer in different planes to learn sizes, topography and structural changes of endocrine glands, to expose in them the presence of anomalies of development, cysts, tumour defeat and others like that.

### TYPICAL CHANGES IN MOUTH CAVITY. ROLE OF DOCTOR-DENTIST IN EARLY DIAGNOSTICS OF THESE DISEASES.

The diseases of the endocrine system in many cases cause the characteristic changes of facial skeleton, teeth, gums and mucus shell of mouth cavity.

More frequent all it is in the case of the most widespread endocrine disease — *diabetes mellitus* which shows up *the syndrome of chronic hyperglycemia*. The first clinical signs of this disease can be looked after in a mouth cavity, when patiently dryness in a company appears, in tongue the amount of threadlike diminishes and is increased – mushroom-like papillae. Such signs must prompt to the doctor-dentist authenticity of disease on diabetes mellitus. It is often there is a plural caries.

Swinging majority of patients suffers on parodontose, infectious and mycotic defeats of mucus shell of mouth cavity as a result of decline of general and local immunity. More frequent all there is catarrhal gingivitis, both sharp and chronic, possible development of haemorrhagic defeat of gums. There is red flat lichen.

In such cases, when is the grounds to suspect diabetes mellitus at a patient, dentist must point him at the analysis of glucose of blood and on consultation to the internist. Timely treatment of diseases of teeth and gums at patients with diabetes mellitus diminishes the amount of complications, improves the function of digestion. Set of prosthetic teeth to these patients must be executed with the special exactness for the sake of prevention to formation of bedsores.

In the case of *thyreotoxicose patients often grumble about heartburn of mucus shell of cavity of mouth, decline or loss of the taste feelings which are the display of glossitis. They have the signs of parodontites, exfoliative cheilitis. Teeth it is are often struck by caries; there is the rapid pathological wipe of enamel. Caries is mostly localized in a region on frontal teeth and is quickly made progress.*

In the case of *syndrome of hypothyreosis and his extreme displays - mixedema at a patient arises up characteristic changes in a personality, conductness and voice. Therefore have a considerable diagnostic value supervision of doctor-dentist during many years. In such patient is multiplied a tongue due to the mucus edema, that is reflected by the imprints of teeth and incomplete closing of the mouth. Mucus shells of mouth cavity pinky, brilliant, hypertrophied. A plural caries develops.*

Suspecting the disease of thyroid gland, a doctor-dentist needs to send a patient to endocrinology, accounting to him for the possible reasons of origin of jaw-facial pathology. It is needed to caution people at age years, patients on hypothyreos, from supercooling which can entail *coma*.

Every stomatologist must know that parathyroid glands produce **hormone**, which together with the D3 vitamin supports normal maintenance of calcium in a blood. In the case of operations on a thyroid gland as a result of casual or erroneous delete of parathyroid glands or autoimmune defeat of the last possible origin of sharp clinical signs **of hypoparathyroid** with the critical decline of maintenance of calcium in a blood (*hypocalciemia*) and origin *of convulsive syndrome*. Help in these case is intravenous introduction of chloride or gluconate of calcium. In the case of moderate hypoparathyroid patients feel pricking in a language, involvement of lips, report of jaws, heartburn and dryness in a company. They are disturbed the frequent diseases of parodont: gingivitis, parodontitis and parodontoses.

In the case of tumours of parathyroid glands which excrete parathormone, the phenomena **of hypoparathyroidism with the origin of plural cysts in bones develop, in particular, in jaws, that conduces to their spontaneous breaks. There is characteristic formation of stone in buds, gall-bladder and channels of salivary glands as a result of considerable hypercalciemia.**

In the case of origin of suspicion on pathology of parathyroid glands maintenance of calcium and phosphorus is determined in a blood, and a patient is sent to endocrinology. In case of origin of attack of cramps a stomatologist must give exigent help to the patient, to cause an ambulance and send him to the nearest hospital.

In the case of *chronic adrenal insufficiency* which shows up **the Addison disease**, the deposit of dark pigment under the mucus shell of tongue and lips is characteristic.

This sign is so noticeable and specific, that, exposing her, a stomatologist must quickly send a patient to endocrinology, and in sharp case – to hospitalize to endocrinology hospital.

In the case of **hypercorticism**, a stomatologist often appear the characteristic **edema of mucus shell of cavity of mouth, erosions, haemorrhagic blisters. There are the candida defeats of mucus shell, which show up white or whiter-grayish stratifications which are easily taken off. The characteristic general view of patient, anamnesis and pathological changes of mucus shell of mouth cavity allow dentist as first to expose this disease and send patient to endocrinology.**

– There are very characteristic changes of jaw-face region at patients with **acromegaly**. As a result of increase of lower jaw there is prognaty. It is multiplied a tongue (*macroglossitis*) and lips also (*macrocheilitis*). *Baby's dummies of tongue are hypertrophied, and the mucus shell of mouth cavity becomes dense and is not going to the folds. Characteristic original appearance of patient next to the changes of jaw-facial region serve as foundation of direction of him to the doctor-endocrinologist.*

## Basic syndromes in endocrinology

### Hyperglycemia (Diabetes Mellitus)

*A syndrome characterized by hyperglycemia resulting from absolute or relative impairment in insulin secretion and/or insulin action.*

**Type I DM:** Although it may occur at any age, type I DM most commonly develops in childhood or adolescence and is the predominant type of DM diagnosed before age 30. This type of diabetes accounts for 10 to 15% of all cases of DM and is characterized clinically by hyperglycemia and a propensity to DKA. The pancreas produces little or no insulin.

About 80% of patients with type I DM have specific HLA phenotypes associated with detectable serum islet cell cytoplasmic antibodies and islet cell surface antibodies (antibodies to glutamic acid decarboxylase and to insulin are found in a similar proportion of cases).

**Type II DM:** Type II DM is usually the type of diabetes diagnosed in patients > 30 yr, but it also occurs in children and adolescents. It is characterized clinically by hyperglycemia and insulin resistance. DKA is rare. Although most patients are treated with diet, exercise, and oral drugs, some patients intermittently or persistently require insulin to control symptomatic hyperglycemia and prevent NHHHC. The concordance rate for type II DM in monozygotic twins > 90%. Type II DM is commonly associated with obesity, especially of the upper body (visceral/abdominal), and often presents after a period of weight gain. Impaired glucose tolerance associated with aging is closely correlated with the typical weight gain. Type II DM patients with visceral/abdominal obesity may have normal glucose levels after losing weight.

Type II DM is a heterogeneous group of disorders in which hyperglycemia results from both an impaired insulin secretory response to glucose and decreased insulin effectiveness in stimulating glucose uptake by skeletal muscle and in restraining hepatic glucose production (**insulin resistance**). However, insulin resistance is common, and most patients with insulin resistance will not develop diabetes, because the body compensates by adequately increasing insulin secretion. Insulin resistance in the common variety of type II DM is not the result of genetic alterations in the insulin receptor or the glucose transporter. However, genetically determined postreceptor intracellular defects likely play a role. The resulting hyperinsulinemia may lead to other common conditions, such as obesity (abdominal), hypertension, hyperlipidemia, and coronary artery disease (**the syndrome of insulin resistance**).

## Symptoms and Signs

DM has diverse initial presentations. Type I DM usually presents with symptomatic hyperglycemia or DKA. Type II DM may present with symptomatic hyperglycemia, but is frequently diagnosed in asymptomatic patients during a routine medical examination or when patients present with clinical manifestations of a late complication.

Often following the acute onset of type I DM, there is substantial secretion of insulin. Type I DM patients may experience a honeymoon period characterized by a long phase of near-normal glucose levels without any treatment.

**Symptomatic hyperglycemia:** **Polyuria** followed by **polydipsia**, **poliphagia** and **weight loss** occur when elevated plasma glucose levels cause marked glucosuria and an osmotic diuresis, resulting in **dehydration**. Hyperglycemia may also cause blurred vision, fatigue, and nausea and lead to various fungal and bacterial infections. In type II DM, symptomatic hyperglycemia may persist for days or weeks before medical attention is sought; in women, type II DM with symptomatic hyperglycemia is frequently associated with itching due to vaginal candidiasis.

**Late complications:** Late complications occur after several years of poorly controlled hyperglycemia. Glucose levels are increased in all cells except where there is insulin-mediated glucose uptake (mainly muscle), resulting in an increase in glycolysis and in the activity of other metabolic pathways, which may be caused by complications. Most microvascular complications can be delayed, prevented, or even reversed by tight glycemic control, ie, achieving near-normal fasting and postprandial glucose levels, reflected by near-normal glycosylated hemoglobin (Hb A<sub>1c</sub>). Macrovascular disease such as atherosclerosis may lead to symptomatic coronary artery disease, claudication, skin breakdown, and infections. Although hyperglycemia may accelerate atherosclerosis, many years of hyperinsulinemia preceding the onset of diabetes (with insulin resistance) may play a major initiating role. Amputation of a lower limb for severe peripheral vascular disease, intermittent claudication, and gangrene remains common. Background **retinopathy** (the initial retinal changes seen on ophthalmoscopic examination or in retinal photographs) does not significantly alter vision, but it can progress to macular edema or proliferative retinopathy with retinal detachment or hemorrhage, which can cause blindness. About 85% of all diabetics eventually develop some degree of retinopathy.

Diabetic **nephropathy** develops in about one third of type I DM patients and in a smaller percentage of type II DM patients. In patients with type I DM, GFR may be increased initially with hyperglycemia. After about 5 yr of type I DM, clinically detectable albuminuria ( $\geq 300$  mg/L), which is unexplained by other urinary tract disease, may develop. **Albuminuria** signals a progressive decrease in GFR with a high likelihood of development of end-stage renal disease within 3 to 20 yr

(median, 10 yr). Albuminuria is almost 2.5 times higher in type I DM patients with diastolic BP > 90 mm Hg than in those with diastolic BP < 70 mm Hg. Thus, both hyperglycemia and hypertension accelerate the progression to end-stage renal disease. Diabetic nephropathy is usually asymptomatic until end-stage renal disease develops, but it can cause the nephrotic syndrome. Albuminuria and renal disease may be prevented or delayed with the ACE inhibitor captopril. While aggressive treatment of hypertension prevents the deterioration of renal function, ACE inhibitors have shown added benefits over other classes of antihypertensives. In fact, ACE inhibitors prevent proteinuria in hypertensive and nonhypertensive diabetics. Recent evidence suggests that ACE inhibitors also help prevent retinopathy.

Diabetic neuropathy commonly occurs as a distal, symmetric, predominantly sensory **polyneuropathy** that causes sensory deficits, which begin with and are usually most marked by a stocking-glove distribution. Diabetic polyneuropathy may cause numbness, tingling, and paresthesias in the extremities and, less often, debilitating, severe, deep-seated pain and hyperesthesias. Ankle jerks are usually decreased or absent. Other causes of polyneuropathy must be excluded (see [Ch. 183](#)). Acute, painful **mononeuropathies** affecting the 3rd, 4th, or 6th cranial nerve as well as other nerves, such as the femoral, may spontaneously improve over weeks to months, occur more frequently in older diabetics, and are attributed to nerve infarctions. **Autonomic neuropathy** occurs primarily in diabetics with polyneuropathy and can cause postural hypotension, disordered sweating, impotence and retrograde ejaculation in men, impaired bladder function, delayed gastric emptying (sometimes with dumping syndrome), esophageal dysfunction, constipation or diarrhea, and nocturnal diarrhea. A decrease in heart rate response to the Valsalva maneuver or on standing and unchanged heart rate variation during deep breathing are evidence of autonomic neuropathy in diabetics.

**Foot ulcers and joint problems** are important causes of morbidity in DM. The major predisposing cause is diabetic polyneuropathy--the sensory denervation impairs the perception of trauma from such common causes as ill-fitting shoes or pebbles. Alterations in proprioception lead to an abnormal pattern of weight bearing and sometimes to the development of Charcot's joints.

The risk of **infection** from fungi and bacteria is increased because of decreased cellular immunity caused by acute hyperglycemia and circulatory deficits caused by chronic hyperglycemia. Peripheral skin infections and oral and vaginal thrush are most common. A mycotic infection may be the initial process, leading to wet interdigital lesions, cracks, fissures, and ulcerations that favor secondary bacterial invasion. Patients with infected foot ulcers frequently feel no pain because of neuropathy and have no systemic symptoms until late in a neglected course. Deep ulcers and particularly ulcers associated with any detectable cellulitis require immediate hospitalization, since systemic toxicity and permanent disability may develop. Osteomyelitis should be ruled out by bone scan. Early surgical

debridement is an essential part of management, but amputation is sometimes necessary.

## Diagnosis

In asymptomatic patients, DM is established when the diagnostic criterion for fasting hyperglycemia recommended by the National Diabetes Data Group (NDDG) is met: a plasma (or serum) glucose level of  $\geq 140$  mg/dL ( $\geq 7.77$  mmol/L) after an overnight fast on two occasions in an adult or child. Recently, the American Diabetes Association recommended that fasting plasma glucose levels of  $> 126$  mg/dL ( $> 6.99$  mmol/L) be considered diagnostic for DM.

An **oral glucose tolerance test** (OGTT) may be helpful in diagnosing type II DM in patients whose fasting glucose is between 115 and 140 mg/dL (6.38 and 7.77 mmol/L) and in those with a clinical condition that might be related to undiagnosed DM (eg, polyneuropathy, retinopathy). However, various conditions other than DM, such as effects of drugs, and normal aging can cause abnormalities in the OGTT.

The NDDG also recommends criteria for the diagnosis of **impaired glucose tolerance** in patients who do not meet the OGTT diagnostic criteria for DM. Patients with impaired glucose tolerance may be at increased risk of developing fasting or symptomatic hyperglycemia, but in many patients the condition does not progress or it resolves.

## Thyrotoxicosis

Most symptoms and signs of hyperthyroidism are the same for all types with some exceptions, such as infiltrative ophthalmopathy (common) and dermopathy (uncommon), which are autoendocrine manifestations of Graves' disease and are not seen in other causes.

The clinical presentation of hyperthyroidism may be dramatic or subtle. Common signs and symptoms are *goiter; tachycardia; widened pulse pressure; warm, fine, moist skin; tremor; eye signs (see below); atrial fibrillation; nervousness and increased activity; increased sweating; hypersensitivity to heat; palpitations; fatigue; increased appetite; weight loss; insomnia; weakness; and frequent bowel movements (occasionally diarrhea).*

**Eye signs** noted in patients with hyperthyroidism include stare, lid lag, lid retraction, and mild degrees of conjunctival injection. These eye signs are largely due to excessive adrenergic stimulation and usually remit with successful treatment. Infiltrative ophthalmopathy is a more serious development and is specific to Graves' disease. It is characterized by orbital pain, lacrimation, irritation, photophobia, increased retro-orbital tissue, exophthalmos, and

lymphocytic infiltration of the extraocular muscles which can produce ocular muscle weakness frequently leading to double vision.

Infiltrative dermopathy, also called pretibial myxedema (a confusing term, because myxedema suggests hypothyroidism), is characterized by nonpitting infiltration by proteinaceous ground substance, usually in the pretibial area. It rarely occurs in the absence of Graves' ophthalmopathy. The lesion is often pruritic and erythematous in its early stages and subsequently becomes brawny. Like ophthalmopathy, infiltrative dermopathy may appear years before or after hyperthyroidism.

**Thyroid storm** is characterized by the abrupt onset of more florid symptoms of hyperthyroidism, with some exacerbated symptoms and atypical signs. Included are fever; marked weakness and muscle wasting; extreme restlessness with wide emotional swings; confusion, psychosis, or even coma; and hepatomegaly with mild jaundice. The patient may present with cardiovascular collapse and shock. Thyroid storm, which is rare in children, results from untreated or inadequately treated hyperthyroidism and may be precipitated by infection, trauma, a surgical procedure, embolism, diabetic acidosis, or toxemia of pregnancy or labor. *Thyroid storm is a life-threatening emergency requiring prompt and specific treatment.*

## Diagnosis

The diagnosis of hyperthyroidism is usually straightforward and depends on a detailed clinical history and physical examination, a high index of suspicion, and routine thyroid hormone function tests. A serum TSH is the best first test, because TSH is always suppressed in hyperthyroid patients except when the etiology is a TSH-secreting pituitary tumor or pituitary resistance to thyroid hormone. Free T<sub>4</sub> should then be measured, and if normal, serum T<sub>3</sub> should be measured (see above).

## Hypothyroidism

### Symptoms and Signs

The symptoms and signs of primary hypothyroidism are generally in striking contrast to those of hyperthyroidism and may be quite subtle and insidious in onset. *The facial expression is dull; the voice is hoarse and speech is slow; facial puffiness and periorbital swelling occur due to infiltration with the mucopolysaccharides hyaluronic acid and chondroitin sulfate; cold intolerance may be prominent; eyelids droop because of decreased adrenergic drive; hair is sparse, coarse, and dry; and the skin is coarse, dry, scaly, and thick. Weight gain is modest and is largely the result of decreased metabolism of food and fluid retention. Patients are forgetful and show other evidence of intellectual impairment, with a gradual change in personality. Some appear depressed. There may be frank psychosis (myxedema madness).*

*There is often carotenemia, particularly notable on the palms and soles, caused by deposition of carotene in the lipid-rich epidermal layers. Deposition of proteinaceous ground substance in the tongue may produce macroglossia. A decrease in both thyroid hormone and adrenergic stimulation causes bradycardia. The heart may be enlarged, partly because of dilation but chiefly because of the accumulation of a serous effusion of high protein content in the pericardial sac. Pleural or abdominal effusions may be noted. The pericardial and pleural effusions develop slowly, and only rarely result in respiratory or hemodynamic distress. Patients generally note constipation, which may be severe. Paresthesias of the hands and feet are common, often due to carpal-tarsal tunnel syndrome caused by deposition of proteinaceous ground substance in the ligaments around the wrist and ankle, producing nerve compression. The reflexes may be very helpful diagnostically because of the brisk contraction and the slow relaxation time. Women with hypothyroidism often develop menorrhagia, in contrast to the hypomenorrhea of hyperthyroidism. Hypothermia is commonly noted. Anemia is often present, usually normocytic-normochromic and of unknown etiology, but it may be hypochromic owing to menorrhagia, and sometimes macrocytic because of associated pernicious anemia or decreased absorption of folic acid. In general, the anemia is rarely severe ( $Hb > 9$  g/dL). As the hypometabolic state is corrected, the anemia subsides, sometimes requiring 6 to 9 mo.*

**Myxedema coma** is a life-threatening complication of hypothyroidism. Its characteristics include a background of long-standing hypothyroidism, coma with extreme hypothermia (temperatures 24 to 32.2° C [75.2 to 90° F]), areflexia, seizures, CO<sub>2</sub> retention, and respiratory depression. Severe hypothermia may be missed unless special low-reading thermometers are used. Rapid diagnosis based on clinical judgment, history, and physical examination is imperative because early death is likely. Precipitating factors include exposure to cold, disease, infection, trauma, and drugs that suppress the CNS.

**Laboratory evaluation** demonstrates a low level of circulating TSH in secondary hypothyroidism (although serum TSH may be normal by immunoassay but with decreased bioactivity), whereas in primary hypothyroidism there is no feedback inhibition of the intact pituitary, and serum TSH levels are elevated. The serum TSH is the simplest and most sensitive test for the diagnosis of primary hypothyroidism. Serum cholesterol is usually high in primary hypothyroidism but less so in secondary hypothyroidism. Other pituitary hormones and their corresponding target tissue hormones may be low in secondary hypothyroidism.

The **determination of total serum T<sub>3</sub>** levels in hypothyroidism deserves mention. In addition to primary and secondary hypothyroidism, other conditions are characterized by decreased circulating levels of total T<sub>3</sub>; these include decreased serum TBG, the effects of some drugs (see above), and the euthyroid patient syndrome due to acute and chronic disease, starvation, and low carbohydrate diets (see above for discussion of euthyroid patient syndrome).

In more severe hypothyroidism, both serum  $T_3$  and  $T_4$  levels are decreased. However, many patients with primary hypothyroidism (elevated serum TSH, low serum  $T_4$ ) may have normal circulating levels of  $T_3$  probably caused by sustained TSH stimulation of the failing thyroid, resulting in preferential synthesis and secretion of the biologically active hormone  $T_3$ .

## Hypocorticism

### Symptoms and Signs

Weakness, fatigue, and orthostatic hypotension are early symptoms. Pigmentation is usually increased except in adrenal insufficiency secondary to pituitary failure. Increased pigmentation (hyperpigmentation) is characterized by diffuse tanning of both exposed and unexposed portions of the body, especially on pressure points (bony prominences), skinfolds, scars, and extensor surfaces. Common are black freckles over the forehead, face, neck, and shoulders; areas of vitiligo; and bluish black discolorations of the areolae and of the mucous membranes of the lips, mouth, rectum, and vagina. Anorexia, nausea, vomiting, and diarrhea often occur. A decreased tolerance to cold, with hypometabolism, may be noted. Dizziness and syncope may occur. ECG may show decreased voltage and prolonged PR and QT intervals. The EEG shows a generalized slowing of the  $\alpha$  rhythm. The gradual onset and nonspecific nature of early symptoms often lead to an incorrect initial diagnosis of neurosis. Weight loss, dehydration, hypotension, and small heart size are characteristic of the later stages of Addison's disease.

An **adrenal crisis** is characterized by profound asthenia; severe pains in the abdomen, lower back, or legs; peripheral vascular collapse; and, finally, renal shutdown with azotemia. Body temperature may be subnormal, although severe hyperthermia due to infection often occurs. Crisis is precipitated most often by acute infection (especially with septicemia), trauma, operative procedures, and Na loss due to excessive sweating during hot weather.

### Laboratory Findings

Abnormal serum electrolyte levels, including low Na ( $< 130$  mEq/L), high K ( $> 5$  mEq/L), low  $HCO_3$  (15 to 20 mEq/L) and high BUN, together with a characteristic clinical picture, suggest Addison's disease (see [Table 9-1](#)). The plasma renin and ACTH levels are increased. When adrenal failure is caused by inadequate ACTH production by the pituitary gland, electrolyte levels are usually normal.

**Testing for adrenal insufficiency:** Testing is performed by injecting cosyntropin 5 to 250  $\mu$ g IV. Normal preinjection plasma cortisol ranges from 5 to 25  $\mu$ g/dL (138 to 690 nmol/L) and doubles at 30 to 90 min, with a minimum of 20  $\mu$ g/dL (552 nmol/L). Patients with Addison's disease have low or normal values that do not rise.

## Diagnosis

Addison's disease is usually suspected after the discovery of hyperpigmentation, although in some patients this may be minimal. In the early stages of the disease, weakness, although prominent, is benefited by rest, unlike neuropsychiatric weaknesses, which are often worse in the morning than after activity. Most myopathies can be differentiated by their distribution and the lack of pigmentation and by characteristic laboratory findings. Patients with hypoglycemia due to oversecretion of insulin may have attacks at any time, usually have increased appetite with weight gain, and have normal adrenal function. Patients with adrenal insufficiency develop hypoglycemia after fasting because of their decreased ability to carry out gluconeogenesis.. Hyperpigmentation due to bronchogenic carcinoma, ingestion of heavy metals such as iron or silver, chronic skin conditions, or hemochromatosis should be considered. The characteristic pigmentation of the buccal and rectal mucosa seen in Peutz-Jeghers syndrome should not cause confusion. Frequently, vitiligo is associated with hyperpigmentation, which may be a helpful indication of Addison's disease, although other diseases can cause this association.

## Adrenal Cortical Hyperfunction

Hypersecretion of one or more adrenocortical hormones produces distinct clinical syndromes. Excessive production of androgens results in adrenal virilism; hypersecretion of glucocorticoids produces Cushing's syndrome; and excess aldosterone output results in hyperaldosteronism (aldosteronism). These syndromes frequently have overlapping features. Adrenal hyperfunction may be compensatory, as in congenital adrenal hyperplasia, or may be due to acquired hyperplasia, adenomas, or adenocarcinomas.

### ***CUSHING'S SYNDROME***

*A constellation of clinical abnormalities due to chronic exposure to excesses of cortisol (the major adrenocorticoid) or related corticosteroids*

### **Symptoms and Signs**

Clinical manifestations include rounded "moon" facies with a plethoric appearance. There is truncal obesity with prominent supraclavicular and dorsal cervical fat pads ("buffalo hump"); the distal extremities and fingers are usually quite slender. Muscle wasting and weakness are present. The skin is thin and atrophic, with poor wound healing and easy bruising. Purple striae may appear on the abdomen. Hypertension, renal calculi, osteoporosis, glucose intolerance, reduced resistance to infection, and psychiatric disturbances are common. Cessation of linear growth is characteristic in children. Females usually have menstrual irregularities. In adrenal tumors, an increased production of androgens,

in addition to cortisol, may lead to hypertrichosis, temporal balding, and other signs of virilism in the female.

## Diagnosis

**Plasma cortisol** is normally 5 to 25  $\mu\text{g/dL}$  (138 to 690  $\text{nmol/L}$ ) in the early morning hours (6 to 8 am) and declines gradually to  $< 10 \mu\text{g/dL}$  ( $< 276 \text{ nmol/L}$ ) in the evening (6 pm and later). Patients with Cushing's syndrome usually have elevated morning cortisol levels and lack the normal diurnal decline in cortisol production, so that evening plasma cortisol levels are above normal and total 24-h cortisol production is elevated. Single plasma cortisol samples may be difficult to interpret because of the episodic secretion that produces the wide range in normal values. Plasma cortisol may be spuriously elevated in patients with congenital increases of corticosteroid-binding globulin, but diurnal variation is normal in these patients. Free **urinary cortisol**, the best assay for urinary excretion (normal 20 to 100  $\mu\text{g/24 h}$  [55.2 to 276  $\text{nmol/24 h}$ ]), is elevated  $> 120 \mu\text{g/24 h}$  ( $> 331 \text{ nmol/24 h}$ ) in Cushing's patients and is only minimally increased in obese patients, in whom it is  $< 150 \mu\text{g/24 h}$  ( $< 414 \text{ nmol/24 h}$ ).

Traditionally, the **dexamethasone test**, in which 1 mg of dexamethasone is administered orally at 11 to 12 pm and plasma cortisol is measured at 7 to 8 am the next morning, has been used to screen for Cushing's syndrome. Most normal patients will suppress their morning plasma cortisol to  $\leq 5 \mu\text{g/dL}$  ( $\leq 138 \text{ nmol/L}$ ) after this test, whereas most patients with nonpituitary Cushing's syndrome will have a morning cortisol level of at least 9  $\mu\text{g/dL}$  (248  $\text{nmol/L}$ ) and will maintain their plasma cortisol at its original level.

## **HYPERALDOSTERONISM** (*Aldosteronism*)

### *The clinical syndrome resulting from excess aldosterone secretion.*

Aldosterone is the most potent mineralocorticoid produced by the adrenals. It causes Na retention and K loss. In the kidney, aldosterone causes transfer of Na from the lumen of the distal tubule into the tubular cells in exchange for K and hydrogen. The same effect occurs in the salivary glands, sweat glands, and cells of the intestinal mucosa and in exchanges between intra- and extracellular fluids.

Aldosterone secretion is regulated by the **renin-angiotensin mechanism** and to a lesser extent by ACTH. Renin, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidney. Reduction in blood volume and flow in the afferent renal arterioles induces renin secretion. Renin causes transformation of angiotensinogen (an  $\alpha_2$  globulin) in the liver to angiotensin I, a 10-amino acid polypeptide, which is converted to angiotensin II, an 8-amino acid polypeptide. Angiotensin II causes secretion of aldosterone and, to a much lesser extent, secretion of cortisol and deoxycorticosterone. The Na and water retention resulting

from increased aldosterone secretion increases the blood volume and reduces renin secretion. Aldosterone is measured by radioimmunoassay.

### ***Primary Aldosteronism (Conn's Syndrome)***

Primary aldosteronism is due to an adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex or, more rarely, to an adrenal carcinoma or hyperplasia. Adenomas are extremely rare in children, but the syndrome is sometimes part of the pattern in childhood adrenal carcinoma or adrenal hyperplasia. The clinical picture is also mimicked by congenital adrenal hyperplasia from deficiency of 11  $\beta$ -hydroxylase. In children, the hypokalemia and hyperaldosteronism of Bartter's syndrome are distinguished from Conn's syndrome by the absence of hypertension.

### **Symptoms and Signs**

Hypersecretion of aldosterone may result in hypernatremia, hyperchlorhydria, hypervolemia, and a hypokalemic alkalosis manifested by episodic weakness, paresthesias, transient paralysis, and tetany. Diastolic hypertension and a hypokalemic nephropathy with polyuria and polydipsia are common. Aldosterone excretion on a high Na intake ( $> 10$  g/day) is usually  $> 200$   $\mu$ g/day if a tumor is present. Deprivation of Na causes K retention. Personality disturbances, hyperglycemia, and glycosuria occasionally occur. In many cases, the only manifestation is mild to moderate hypertension.

### **Diagnosis**

A helpful test is to give spironolactone 200 to 400 mg/day po because it reverses the manifestations of the disease, including hypertension, within 5 to 8 wk. (This reversal rarely occurs in patients with hypertension not due to increased aldosterone.) Measuring plasma renin is helpful in the diagnosis and is usually performed by determining the plasma renin level in the morning with the patient recumbent, giving furosemide 80 mg po, and then repeating the renin determination after the patient has remained upright for 3 h. Normal persons will have a marked increase in renin in the upright position, whereas the patient with hyperaldosteronism will not. About 20% of patients with essential hypertension who do not necessarily have hyperaldosteronism have a low renin that does not respond to the upright position. Measurements of plasma aldosterone, either peripherally or after catheterization of the adrenal veins, may be helpful. Diagnosis is thus dependent on demonstrating elevated aldosterone secretion in urine or blood, expansion of the extracellular space as demonstrated by lack of increase in plasma renin in the upright posture, and the K abnormalities noted. CT often demonstrates a small adenoma in these cases. MRI does not improve diagnostic capability.

## **Pheochromocytoma**

*A tumor of chromaffin cells that secrete catecholamines, causing hypertension.*

In about 80% of cases, pheochromocytomas are found in the adrenal medulla, but they may also be found in other tissues derived from neural crest cells (see Pathology, below). Those in the adrenal medulla appear equally in both sexes, are bilateral in 10% of cases (20% in children), and are usually benign (95%). Extra-adrenal tumors are more often malignant (30%). Although pheochromocytomas may occur at any age, the maximum incidence is between the 3rd and 5th decades.

### **Pathology**

Pheochromocytomas vary in size but average only 5 to 6 cm in diameter. They usually weigh 50 to 200 g, but tumors weighing several kilograms have been reported. Rarely, they are large enough to be palpated or cause symptoms due to pressure or obstruction. The tumor is usually a well-encapsulated nest of chromaffin cells that appear malignant upon microscopic examination.

### **Symptoms and Signs**

The most prominent feature is hypertension, which may be paroxysmal (45%) or persistent (50%) and is rarely absent (5%). About 1/1000 hypertensive patients has a pheochromocytoma. The hypertension is due to secretion of one or more of the catecholamine hormones or precursors: norepinephrine, epinephrine, dopamine, or dopa. Common symptoms and signs are tachycardia, diaphoresis, postural hypotension, tachypnea, flushing, cold and clammy skin, severe headache, angina, palpitation, nausea, vomiting, epigastric pain, visual disturbances, dyspnea, paresthesias, constipation, and a sense of impending doom. Paroxysmal attacks may be provoked by palpation of the tumor, postural changes, abdominal compression or massage, induction of anesthesia, emotional trauma,  $\beta$ -blockers, and micturition if the tumor is in the bladder.

Physical examination, except for the common finding of hypertension, is usually normal, unless performed during a paroxysmal attack. The severity of retinopathy and cardiomegaly is often less extensive than might be expected for the degree of hypertension present.

### **Diagnosis**

The principal urinary metabolic products of epinephrine and norepinephrine are the metanephrines, vanillylmandelic acid (VMA), and homovanillic acid (HVA). Normal persons excrete only very small amounts of these substances in the urine. Normal values for 24 h are as follows: free epinephrine and norepinephrine < 100  $\mu$ g (< 582 nmol), total metanephrine < 1.3 mg (< 7.1  $\mu$ mol), VMA < 10 mg (< 50  $\mu$ mol), and HVA < 15 mg (< 82.4  $\mu$ mol). In pheochromocytoma and

neuroblastoma, urinary excretion of epinephrine and norepinephrine and of their metabolic products increases intermittently.

**Attempts to localize tumors by x-ray** should be limited to multiple views of the chest and abdomen. CT and MRI may be useful, with and without contrast. Positron emission tomography has also been used successfully. IV pyelography with tomography of the perirenal areas should be used only if the previous modalities are unavailable. Phlebography, aortography, and retroperitoneal gas insufflation are contraindicated, as they may induce a serious or fatal paroxysm. Localization of the tumor's level by repeated sampling of plasma catecholamine concentrations during catheterization of the vena cava has been achieved but is also potentially dangerous. Recently, radiopharmaceuticals have been used to localize pheochromocytomas with nuclear imaging techniques. <sup>131</sup>I-metaiodobenzylguanidine (MIBG) is the most studied compound; 0.5 mCi is injected IV and the patient is scanned on days 1, 2, and 3. Normal adrenal tissue rarely picks up this isotope, but 90% of pheochromocytomas do.

### ***HYPERSECRETION OF ANTERIOR PITUITARY HORMONES*** ***(Hyperpituitarism)***

The anterior pituitary hormones that are most commonly secreted in excess are GH (as in acromegaly, gigantism), prolactin (as in galactorrhea), and ACTH (as in the pituitary type of Cushing's syndrome--see also Cushing's Syndrome in Ch. 9).

#### ***Gigantism and Acromegaly***

*Syndromes of excessive secretion of GH (hypersomatotropism) nearly always due to a pituitary adenoma of the somatotrophs.*

Many GH-secreting adenomas contain a mutant form of the G<sub>s</sub> protein, which is a stimulatory regulator of adenylate cyclase. Mutations of the G<sub>s</sub> protein in the somatotrophs bypass the need for GHRH to stimulate GH secretion. A few cases of ectopic GHRH-producing tumors, especially of pancreas and lung, also have been described.

#### **Symptoms and Signs**

Rarely, GH hypersecretion begins in childhood, before closure of the epiphyses, and leads to the exaggerated skeletal growth termed **pituitary gigantism**. GH excess can begin at any age but most commonly starts between the third and fifth decades of life. In children, growth velocity is increased but with little bony deformity. However, soft tissue swelling occurs and the peripheral nerves are enlarged. Delayed puberty or hypogonadotropic hypogonadism is also frequently present, resulting in a eunuchoid habitus. When GH hypersecretion begins after epiphyseal closure, the earliest clinical manifestation is coarsening of the facial features and soft tissue swelling of the hands and feet. The patient's appearance

changes, and larger rings, gloves, and shoes are needed. Photographs of the patient are important in delineating the course of the disease. The increase in dimension of the acral parts has led to the term **acromegaly**.

In adults with acromegaly, other changes also occur. Coarse body hair increases, and the skin thickens and frequently darkens. The size and function of sebaceous and sweat glands increase, such that patients frequently complain of excessive perspiration and an offensive body odor. Overgrowth of the mandible leads to protrusion of the jaw (prognathism) and malocclusion of teeth. Cartilaginous proliferation of the larynx leads to a deep, husky voice. The tongue is frequently enlarged and furrowed. In long-standing acromegaly, costal growth leads to a barrel chest. Articular cartilaginous proliferation occurs early in response to GH excess, with the articular cartilage possibly undergoing necrosis and erosion. Joint symptoms are common, and crippling degenerative arthritis may occur.

### **Posterior Lobe Disorders**

#### ***DIABETES INSIPIDUS***

***(Central Diabetes Insipidus; Vasopressin-Sensitive Diabetes Insipidus)***

*A temporary or chronic disorder of the neurohypophyseal system due to deficiency of vasopressin (ADH) and characterized by excretion of excessive quantities of very dilute (but otherwise normal) urine and by excessive thirst.*

#### **Symptoms and Signs**

Onset may be insidious or abrupt and may occur at any age. The only symptoms in primary DI are polydipsia and polyuria. In acquired forms of DI, symptoms and signs of the associated lesions are also present. Enormous quantities of fluid may be ingested, and large volumes (3 to 30 L/day) of very dilute urine (sp gr usually < 1.005 and osmolality < 200 mOsm/L) are excreted. Nocturia is almost always present in DI and in NDI. Dehydration and hypovolemia may develop rapidly if urinary losses are not continuously replaced.

## Study question

Which from the stated below symptoms, concepts, terms mostly belong physiology and pathology:

- A. Pancreatic islets
- B. Thyroid gland
- C. Parathyroid glands
- D. Adrenal glands
- E. Hypophysis

1. Acromegalia
2. Exophthalmia
3. Cramps
4. Insulin
5. Parathormon
6. Glucagon
7. Prolactin
8. 3.3 – 5.5 Mmol/l
9. Ketoacidosis
10. Icenko-Cushing Disease
11. Aldosteron
12. Glucosurea
13. Thyroxin
14. Nephroangiopathia
15. Thyrotropine
16. Gangrene of foot
17. Mixedema
18. Chloride of calcium intravenous at cramps
19. Cortisol
20. Hyperglycemia
21. Cistoso-fibrous osteopathy
22. Adrenalin
23. Proteinurea
24. Iodine
25. Polyuria
26. to 30 l/ day

### Answers and explanations

1.E, 2. B, 3. C, 4. A, 5. C, 6. A, 7. E, 8. A, 9. A, 10. E, 11. D, 12. A, 13. B, 14. A, 15. E, 16. A, 17. B, 18. C, 19. D, 20. A, 21. C, 22. D, 23. A, 24. B, 25. E.

1. Acromegalia (1) - hyperproduction of the somatotropine, Prolactin (7), Icenko-Cushing Disease – hyperproduction of the corticotropine (15). All of them are hormones of anterior lobe of hypophysis. Polyuria to 30 l/ day is symptom of deficit antidiuretic hormone (vasopressine) that concentrate at posterior lobe of hypophysis (25).
2. Thyroxin (13) – hormone of the thyroid gland, Iodine (24) is in it molecule. Exophthalmia(2) , Mixedema(17) – symptoms of disorders of this gland.
3. Cramps(3) – symptom of deficite of calcium by hypoproduction of Parathormon(5), Chloride of calcium intravenous at cramps (18) -
4. Insulin (4) and Glucagon (6) hormones of islets of pancreas 3.3 – 5.5 Mmol /l (8), Hyperglycemia (2 (20) –symptom of diabetes mellitus – deficit of insulin. , Ketoacidosis (9), Nephroangiopathia 14), Gangrene of foot (16) – all are complications of diabetes mellitus,
5. Aldosterone (11), cortisol(19), Adrenaline (22) – all are hormones of adrenal gland.

## 7

## Approach to Patients with Hematological Diseases

**I. COMPOSITION OF THE BLOOD.** Hematology is the study of the blood-forming tissues and circulating blood components. Normally, the functions of the blood are to deliver nutrients, hormones, and oxygen to tissues; to collect and dispose of the wastes from cellular metabolism; to deliver specialized cells to tissues for protection against the external environment; and to prevent leakage by closing holes in blood vessels. The circulating blood accounts for 5%-7% of the total body weight and is composed of two major elements.

### A. Cellular elements

1. **Red blood cells** (RBCs, erythrocytes) are the cells responsible for carrying oxygen and carbon dioxide between the lungs and the tissues via the hemoglobin content in their cytoplasm. The name of the red blood cell reflects the bright red color of the cell that occurs when oxygen is attached to the hemoglobin. The cell is disk-shaped and biconcave. Because **the cell does not have a nucleus**, its life span is limited by its energy supply.
2. **White blood cells** (WBCs, leukocytes) are colorless **nucleated** cells whose primary function is protection against invading organisms. The white blood cell performs its function in one of two ways.

- a. **Phagocytes engulf**, or phagocytize, the pathogenic organism or foreign particle. These cells have the capacity to move from the bloodstream into the tissues where they are needed. Phagocytes can be identified by the histologic staining of their **granules (granulocytes**, such as neutrophils, basophils, eosinophils) or by their **nuclear characteristics (mononuclear cells** in the circulation are monocytes, in tissue are macrophages).
- b. **Immunocytes** are associated with humoral and cell-mediated reactions of the **immune system**. **B and T lymphocytes** are immunocytes in the blood; **plasma cells** are found in the bone marrow.
3. **Platelets** (thrombocytes) are anucleated, disk-shaped cytoplasmic fragments of megakaryocytes, the precursor cells in the bone marrow. Platelets are released into the circulation to prevent leakage or bleeding caused by inherent or acquired defects in blood vessel walls. The cells have a life span of about 1 week.
- B. Fluid elements. Plasma** is the fluid portion of the blood in which the cellular elements are suspended and circulated throughout the body. (**Serum** is the clear fluid that separates from the blood upon coagulation, when all cellular elements are removed.) Plasma has three main components.
  1. **Water** is the main component of blood. Almost 70% of the body is water, most of which is contained in and around cells. The blood plasma maintains the water content of cells in the tissues.
  2. **Electrolytes** in the plasma are essential to cellular function. The important plasma electrolytes are sodium, potassium, chloride, hydrogen, magnesium, and calcium.
  3. **Proteins** are abundant in the plasma. Although highly varied in structure, plasma proteins can be divided into three main functional classes.
    - a. **Coagulation proteins** are primarily involved in keeping the vascular system intact. Proteins that form clots (**procoagulants**) include components of the extrinsic and intrinsic pathways of the coagulation cascade and fibrinogen. Proteins that breakdown excessive coagulation (**anticoagulants**) are components of the fibrinolytic system. The procoagulants and anticoagulants maintain a balance of clot formation and clot dissolution.
    - b. **Proteins with immunologic functions** include **antibodies** (immunoglobulins) and the components of the complement system. These plasma proteins are involved in defending the body against infections caused by invading organisms and against the presence of foreign antigens.
    - c. **Transport proteins** serve several functions.
      - (1) **Osmotic pressure is maintained** in the intravascular space by **albumin**, which prevents excessive leakage of blood fluid extracellularly. This enables the circulation of blood within the vessels and prevents edema.
      - (2) **Binding and transporting** substances to the tissues and **removal of waste products and toxins** in the circulation are also functions of transport proteins.
      - (a) **Transferrin** is a plasma protein that binds and transports iron to the bone

marrow

for production of red blood cells.

(b) **Transcobalamin** is the carrier protein for vitamin B<sub>12</sub>.

(c) **Haptoglobin** protects tissue cells from noxious substances by binding the byprod

ucts of hemoglobin released from senescent or prematurely destroyed red blood cells and transporting the byproducts to the liver for disposal.

(3) **Transportation of lipids, cholesterol, and triglycerides** is carried out by the **lipoproteins**.

**II. PRINCIPLES OF HEMATOLOGIC DIAGNOSIS.** Peripheral blood examination is a routine part of patient evaluation by most physicians, regardless of speciality. Because of its accessibility and close proximity to all tissues, the blood often provides the earliest evidence of changes in the state of health and the development of illness. An understanding of the mechanisms of blood alterations is very important and, together with information collected from a thorough medical history and physical examination, provides for accurate diagnosis and correct therapeutic choices.

**A. History and physical examination.** Information about the patient's present and past health, genetic makeup, and environmental influences as well as specific details regarding the signs and symptoms of the present illness form the basis for further diagnostic evaluation.

### 1. History

#### a. Medical history

(1) The **present illness** should be the focus of the medical history, with an emphasis on the following:

(a) Bleeding

(b) Infections or symptoms related to enlargement of lymph nodes, the liver, or the spleen

(c) Nonspecific symptoms related to anemia (e.g., malaise, weakness, headache, weight loss)

(2) Any **exposure to drugs or chemicals** should be determined since such agents may cause or worsen many hematologic disorders (e.g., hemolysis, neutropenia, thrombocytopenia, myeloproliferative disorders).

(3) A **review of systems** (including the nervous system) is necessary, since blood dyscrasia affects many, if not all, organ systems.

**b. Family history.** Information about the health of family members as well as the ethnic background of the patient is important in certain inherited hematologic conditions, notably sickle cell anemia and the thalassemias.

### 2. Physical Examination

Physical examination may produce abnormal assessment findings in various body systems, caused by anemia, uncontrolled bleeding or clotting, or altered immune function that leads to infection in patients with hematologic disorders. Perform a systematic physical examination, paying careful attention to the cardiovascular,

respiratory, and integumentary systems.

- a. Thorough physical examination of the hematologic patient is important and should focus closely on the skin and nails, mouth, mucous membranes, and eyes. Jaundice, pallor, cyanosis, petechiae and ecchymoses, excoriations, and ulcers are common findings.
- b. Hepatomegaly, splenomegaly, enlarged or tender lymph nodes, soreness over the ribs or sternum, and a variety of neurologic abnormalities are common in hematologic disorders.

### 3. Peripheral blood measurements.

Information about the number of cellular components and about the concentration of plasma components is extremely useful to all clinicians.

#### 1. Peripheral blood counts and measurements

**a. Red cell count and hematocrit (Hct).** The hematocrit is the proportion of the blood occupied by red cells. It can be measured manually or by electronic instruments.

- (1) The hematocrit is determined manually by centrifuging a volume of anticoagulated blood in a 3-mm tube (macro scale) or a capillary tube (micro scale) and measuring the volume of packed red cells at the bottom of the tube. The hematocrit is expressed as a percentage.

**b. Hemoglobin concentration** is most accurately estimated by measuring the light absorbance of cyanmethemoglobin-a stable derivative of hemoglobin-derived by colorimetric methods.

- (1) Manual and automated measurements of cyanmethemoglobin concentration provide comparable estimates of hemoglobin concentration.
- (2) The red cell volume is approximated by the hemoglobin concentration and hematocrit level, and each should be used as a check of the other to avoid laboratory error. However, since the method for measuring hemoglobin is more precise and the hemoglobin concentration is measured directly in contrast to the hematocrit, which is calculated indirectly from the MCV, the hemoglobin concentration is the preferred laboratory parameter for evaluating changes in red cells.

**b. Red cell indices** are measurements that indicate the size and hemoglobin content of red

cells. These values can be calculated quantitatively from the hemoglobin concentration,

red cell counts, and packed red cell volume. The accuracy of red cell indices has increased

- (1) **Mean corpuscular volume** refers to the average volume of the individual red cells. The MCV is expressed in cubic micrometers ( $\mu\text{m}^3$ ) per red cell, or femtoliters (fl), and is calculated as follows:

$$(2) \quad \text{MCV} = \frac{\text{packed red cell volume/1000 ml blood}}{\text{red cell count (millions/mm}^3\text{)}}$$

- 2) **Mean corpuscular hemoglobin (MCH)** refers to the hemoglobin content per red cell.

The MCH is expressed in picograms (pg) per red cell and is calculated as follows:

$$\text{MCH} = \frac{\text{hemoglobin (g/1000 ml blood)}}{\text{Red cell count (millions/mm}^3\text{)}}$$

**(3) Mean corpuscular hemoglobin concentration (MCHC)** refers to the hemoglobin concentration of the red cells.

The MCHC is expressed in grams per decaliter of red cells and is calculated as follows:

$$\text{MCHC} = \frac{\text{hemoglobin (g/1000 ml blood)} \times 100}{\text{packed red cell volume (\%)}}$$

**e. Platelet count.** A rough count of platelets in a blood smear can be obtained manually or by machine.

(1) Platelets are anucleated and appear in the peripheral blood smear as small blue bodies, with red or purple granules.

**C. Blood smear examination.** Critical diagnostic information regarding the morphology of the cellular elements of the blood can be obtained through the examination of blood smears. Routinely, morphologic evaluation is performed using a fixed and stained sample of blood cells.

#### **a. Reticulocyte staining**

(1) Immature red cells are identified by supravital staining of precipitated residual RNA

with new methylene blue or brilliant cresyl blue; the cells containing the stained pre

cipitate are counted and reported as a percentage of the red cells examined. (2)

The reticulocyte count is an effective means of assessing red cell production.

#### **b. Heinz body staining**

(1) Heinz bodies are precipitated denatured hemoglobin demonstrated by the supravital staining of red cells with crystal violet.

(2) This test is used to identify unstable hemoglobinopathies, hemolysis due to glucose-6-phosphate dehydrogenase (G6PD) deficiency, and hemoglobin H (Hb H) disease (an  $\alpha$ -thalassemia).

**3. Fixed blood smears.** Examination of a fixed peripheral blood smear stained with Wright's or Giemsa stain allows identification of various changes in blood cell morphology typical of certain diseases. This examination is used to target suspected disease and not as an indicator of general health.

#### **a. Blood cell morphology**

(1) **Red cell morphology.** Red cells should be examined for size, shape, hemoglobin content, staining properties (e.g., polychromatophilia), distribution in the film (e.g., rouleau formation: the stacking of red cells like coins), and inclusion bodies.

(2) **White cell morphology.** The peripheral blood film also should be examined for the presence of immature white cells, a "shift to the left" (i.e., an increase in the number of band neutrophils), hypersegmentation or hyposegmentation of neutrophils, atypical lymphocytes, leukocyte inclusions (e.g., toxic granulations,

Dohle bodies), and the presence of bacteria inside or outside granulocytes.

|  |  |
|--|--|
|  |  |
| Amount of red cells (RBC)                              | $4,5 \pm 1,5 \cdot 10^{12}/l$                  |
| Concentration of haemoglobin (HGB)                     | $145 \pm 25 \text{ g/l}$                       |
| Mean corpuscular volume of red cells (MCV)             | $86 \pm 8 \text{ MKM}^3 \text{ (fl)}$          |
| Mean concentration haemoglobin in red corpuscles (MCH) | $30 \pm 3 \text{ pg}$                          |
| Mean concentration of haemoglobin in red cells (MCHC)  | $325 \pm 25 \text{ g/l}$ ( $33,5 \pm 2,5 \%$ ) |
| Colour index (CI)                                      | $0,86 - 1,05$                                  |
| Amount of reticulocytes (R, Ret)                       | $2 - 15\%$                                     |
| <i>Estimation of thrombocytes (platelets)</i>          |  |
| Amount of <i>platelets</i> (PLT)                       | $150 - 450 \cdot 10^9/l$                       |
| Mean volume of platelets (MPV)                         | $7 - 11 \text{ fl}$                            |
| <i>Estimation of leukocytes</i>                        |  |
| Amount of leukocytes (WBC)                             | $7.5 \pm 3.5 \cdot 10^9/l$                     |
| <i>White blood cells morphology</i>                    |  |
| Segmented neutrophils                                  | $40-70\% (2.2-4.2 \cdot 10^9/l)$               |
| Band neutrophils                                       | $1-5\%$  |
| Eosinophyls  | $1-4\% (0.1-0.3 \cdot 10^9/l)$                 |
| Basophyls  | $0-1\% (\text{to } 0.06 \cdot 10^9/l)$         |
| Monocytes  | $3-8\% (0.2-0.55 \cdot 10^9/l)$                |
| Lymphocytes  | $20-35\%, 1.5-2.8 \cdot 10^9/l$                |

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. Several cellular elements of the blood are anuclear these include all of the following

EXCEPT

(A) erythrocytes

(B) reticulocytes

(C) thrombocytes

(D) leukocytes

2. Automated blood counting systems have advantages over manual counting methods in that they;

(A) do not require an accurate set of dilution factors

(B) are not wholly dependent on technician skills

(C) do not rely on the examination of fixed slides

(D) require precise sampling of the diluted sample

**Directions:** The item below contains four suggested answers, of which **one or more** is correct. Choose the answer

**A** if 1, 2, and 3 are correct **B** if 1 and 3 are correct

**C** if 2 and 4 are correct **D** if 4 is correct

**E** if 1, 2, 3, and 4 are correct

(1) a thalassemia

(2) glucose-6-phosphate dehydrogenase (G6PD) deficiency

(3) unstable hemoglobinopathy

(4) lead intoxication

**Directions:** The group of items in this section consists of lettered options followed by a set of numbered items. For each item, select the **one** lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

### Questions 4-8

For each function of transport proteins, select the associated protein.

(A) Albumin (B) Transferrin (C) Haptoglobin (D) Transcobalamin (E) None of the above

4. Iron transport, 5. Vitamin B<sub>12</sub> transport 6. Clot formation

7. Plasma osmotic pressure maintenance 8. Hemoglobin transport

## ANSWERS AND EXPLANATIONS

### 1. The answer is D [1 A 1, 21].

Leukocytes are among the cellular elements of the blood that retain their nuclei. The erythrocyte (red blood cell) is released from the marrow in its immature form (the reticulocyte) after the cell has extruded its pyknotic nucleus. However, in disease states resulting in severe hemolysis, immature nucleated red cells may be released into the circulation. The platelets (thrombocytes) in the circulation are fragments of the cytoplasm of the megakaryocyte, which is a large cell with a multilobulated nucleus. The megakaryocyte is confined to the bone marrow in normal states. All leukocytes (white blood cells) circulate in the blood with their nuclei intact.

### 2. The answer is B [11 B 1].

The accuracy and reliability of automated counting systems are not wholly dependent on the skill of the technician; the accuracy of manual counting depends on the technician's skill at every step of the procedure. Automated blood counting methods are more accurate and precise, and have greater reproducibility of results, than manual counting methods. It is critical that samples be accurately diluted before either manual or automated counting methods are used. Automated image analysis is dependent on fixed slides, whereas flow cytometry is not.

### 3. The answer is A (1, 2, 3) [11 C 2 b].

Heinz bodies are supravital stained hemoglobin precipitates in the red cell and are found in conditions in which insoluble hemoglobin is present in the red cells. Such conditions include *a* thalassemia with precipitation of the unstable hemoglobin H (Hb H), glucose-6-phosphate dehydrogenase (G6PD) deficiency resulting in oxidative denaturation of hemoglobin into insoluble masses, and unstable hemoglobinopathy in which alpha- ( $\alpha$ -) globin or beta- ( $\beta$ -) globin mutations result in the spontaneous formation of precipitates of hemoglobin. Lead intoxication does not affect the precipitation of hemoglobin in red cells but causes basophilic stippling.

### 4-8. The answers are: 4-B [1 B 3 c(Z)], 5-D [1 B 3 c (2)], 6-E [1 B 3 a], 7-A [1 B 3 c(1)], 8-C [1 B 3 c (2)].

The functions of transport proteins can be divided into three general classes: the control of diffusion into the tissues, the highly specific recognition of molecules, and the removal of toxins. Transferrin helps in transporting iron to storage and utilization sites in the bone marrow. The damage that free iron can cause to tissues other than the marrow is prevented when it is bound by transferrin. Transcobalamin binds to

vitamin B<sub>12</sub>, and prevents it from degrading while it is being transported to storage and utilization sites in tissues with high cellular turnover rates. Albumin is the main plasma protein responsible for the maintenance of serum osmotic pressure. Haptoglobin is a plasma protein that binds free hemoglobin in the blood and delivers it to the liver for recycling. The degree of intravascular hemolysis is determined by measuring the levels of depleted free forms of haptoglobin in the blood.

### ***Key History Questions***

1. What are your present medications? Do you take any over-the-counter medications, vitamins, herbals, or nutritional supplements? What else have you taken in the past several months?
2. What medical problems have you had in the past? Any surgery? Ask specifically about partial or total gastrectomy, splenic injury or splenectomy, tendency to bleed (eg, with dental procedures), infectious diseases, human immunodeficiency virus (HIV) infection, cancer.
3. What is your occupation? Ask about exposure to substances such as benzene, pesticides, and ionizing radiation.
4. Do you have a family history of hematologic or malignant disorder?
5. Determine the social history and lifestyle. Do you use recreational drugs or alcohol? What is your pattern of sexual activity?

## **Main syndromes in hematology**

### **Acute Leukemia**

A usually rapidly progressing leukemia characterized by replacement of normal bone marrow by blast cells of a clone arising from malignant transformation of a hematopoietic stem cell.

The acute leukemias consist of acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML).

Leukemic cells accumulate in the bone marrow, replace normal hematopoietic cells, and spread to the liver, spleen, lymph nodes, CNS, bloods, and gonads. Because the cells are bloodborne, they can infiltrate any organ or site. ALL often involves the CNS, whereas acute monoblastic leukemia involves the gums, and AML involves localized collections in any site (granulocytic sarcomas or chloromas). Leukemic infiltration appears as sheets of undifferentiated round cells with usually minimal disruption of organ function except for the CNS and bone marrow. Meningeal infiltration results in increasing intracranial pressure with papilledema and cranial nerve palsies. Bone marrow infiltration with replacement of normal hematopoiesis causes anemia, thrombocytopenia, and granulocytopenia.

### **Symptoms and Signs**

The presenting symptoms are usually nonspecific (eg, fatigue, fever, malaise, weight loss) and reflect the failure of normal hematopoiesis. The cause of fever is often not found, although granulocytopenia may lead to an obvious and often

severe bacterial infection. Bleeding is usually manifested by petechiae, easy bruisability with mucous membrane hemorrhage (eg, epistaxis), or menstrual irregularity. Hematuria and GI bleeding are uncommon. Initial CNS involvement (causing headaches, vomiting, and irritability) is uncommon. Bone and joint pain sometimes occur, especially in ALL.

### **Laboratory Findings and Diagnosis**

Anemia and thrombocytopenia are very common (75 to 90%). The WBC count may be decreased, normal, or increased. Blast cells are usually found in the blood smear unless the WBC count is markedly decreased. Although the diagnosis can usually be made from the blood smear, bone marrow examination should always be performed. Sometimes bone marrow examination yields such a hypocellular aspirate that a needle biopsy is required. Aplastic anemia, infectious mononucleosis, and vitamin B12 and folate deficiency should be considered in the differential diagnosis of severe pancytopenia.

The blasts of ALL should be distinguished from those of AML by histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies. In addition to smears with the usual stains, terminal transferase, myeloperoxidase, Sudan black B, and specific and nonspecific esterase histochemical stains are frequently helpful.

CNS disease may be the first evidence of relapse of ALL..

In acute promyelocytic leukemia (APL) and some other cases of AML, disseminated intravascular coagulation (DIC) may occur at presentation and worsen as leukemic cell lysis releases procoagulant. In APL, all-trans-retinoic acid will correct the DIC in 2 to 5 days and, when combined with daunorubicin or idarubicin, can achieve remission in 80 to 90% of patients.

Chronic Leukemia

### **CHRONIC LYMPHOCYTIC LEUKEMIA**

(Chronic Lymphatic Leukemia)

Clonal expansion of mature-appearing lymphocytes involving lymph nodes and other lymphoid tissues with progressive infiltration of bone marrow and presence in the peripheral blood.

Seventy-five percent of cases are diagnosed in patients > 60 yr. CLL is twice as common in men. The cause is unknown, but some cases are familial. CLL is rare in Japan and China and does not seem to increase among Japanese expatriates in the USA, suggesting a genetic factor.

### **Symptoms and Signs**

Onset is usually insidious, and CLL is often initially diagnosed from incidental blood tests or during evaluation of asymptomatic lymphadenopathy. The symptomatic patient usually has nonspecific complaints of fatigue, anorexia, weight loss, dyspnea on exertion, or a sense of abdominal fullness (from an enlarging spleen or palpable nodes). Initial findings include generalized lymphadenopathy and minimal-to-moderate hepatomegaly and splenomegaly. With progressive disease, there may be pallor due to anemia. Skin infiltration may be a feature of T-cell CLL patients. A predisposition to bacterial, viral, and fungal

infection occurs in late disease because of hypogammaglobulinemia and granulocytopenia.

#### Laboratory Findings and Diagnosis

The hallmark of CLL is sustained, absolute lymphocytosis ( $> 10,000/\mu\text{L}$ ) and increased lymphocytes ( $> 30\%$ ) in the bone marrow. At diagnosis, uncommonly, there may be moderate anemia and thrombocytopenia because of bone marrow infiltration (10% of cases), splenomegaly, or immunohemolytic anemia and thrombocytopenia. Some patients will have hypogammaglobulinemia ( $< 15\%$  of cases), and occasionally a monoclonal serum immunoglobulin spike of the same type may be found on the leukemic cell surface (2 to 4% of cases).

### **CHRONIC MYELOCYTIC LEUKEMIA**

(Chronic Myeloid, Chronic Myelogenous, or Chronic Granulocytic Leukemia)

Clonal myeloproliferation caused by malignant transformation of a pluripotent stem cell and characterized clinically by striking overproduction of granulocytes. CML may occur in either sex. Although CML can occur at any age, the median age is about 45 yr; it is uncommon before 10 yr of age.

#### Symptoms and Signs

Patients are often asymptomatic early on; CML may be diagnosed during an incidental CBC. In other patients, insidious onset of nonspecific symptoms (eg, fatigue, weakness, anorexia, weight loss, fever, night sweats, a sense of abdominal fullness) may prompt evaluation. Initially, pallor, bleeding, and easy bruisability and lymphadenopathy are unusual, but moderate or occasionally extreme splenomegaly is common (60 to 70% of cases). With disease progression, splenomegaly may increase, and pallor and bleeding occur. Fever, marked lymphadenopathy, and skin involvement are ominous developments.

#### Laboratory Findings

In the asymptomatic patient, the WBC count is usually  $< 50,000/\mu\text{L}$ . In the symptomatic patient, the WBC count is usually about  $200,000/\mu\text{L}$  but may reach  $1,000,000/\mu\text{L}$ . The platelet count is normal or moderately increased, and the Hb is usually  $> 10 \text{ g/dL}$ . On blood smears, all stages of granulocyte differentiation are seen, although in patients with WBC counts  $< 50,000/\mu\text{L}$ , immature granulocytes may be uncommon. The absolute eosinophil and basophil concentrations can be strikingly increased, but the absolute lymphocyte and monocyte concentrations may be normal. A few nucleated RBCs may be present, and blood cell morphology is normal. The bone marrow is hypercellular on aspirate and biopsy. Even at diagnosis, some patients may have some myelofibrosis. The leukocyte alkaline phosphatase score is very low.

The Philadelphia chromosome (Ph, formerly termed Ph1) can be demonstrated in almost all patients (95%) by chromosomal analysis. Although chromosome 22 is often referred to as the Ph chromosome, the correct finding is a reciprocal translocation  $t(9;22)$  with a piece of chromosome 9 containing the oncogene *c-abl* translocated to chromosome 22, where fusion to another gene *bcr* results in a fusion gene (ABL-BCR) and a piece of chromosome 22 translocated to chromosome 9. ABL-BCR is important in the pathogenesis and expression of

CML. In some patients in whom the Ph chromosome is not evident, bcr gene rearrangement can be shown by molecular studies (Southern blot).

CML is relatively easy to diagnose because of associated splenomegaly, leukocytosis with immature granulocytes and absolute eosinophilia and basophilia, low leukocyte alkaline phosphatase levels, and presence of the Ph chromosome. In differential diagnosis, the leukocytosis of patients with myelofibrosis is usually associated with nucleated RBCs, tear-shaped RBCs, anemia, and thrombocytopenia. Myeloid leukemoid reactions resulting from cancer or infection are not associated with the absolute eosinophilia and basophilia and usually have an increased leukocyte alkaline phosphatase score.

## **Hemostasis**

Hemostasis, the arrest of bleeding from an injured blood vessel, requires the combined activity of vascular, platelet, and plasma factors counterbalanced by regulatory mechanisms to limit the accumulation of platelets and fibrin in the area of injury. Hemostatic abnormalities can lead to excessive bleeding or thrombosis.

**Vascular factors:** Vascular factors reduce blood flow from trauma by local vasoconstriction (an immediate reaction to injury) and compression of injured vessels by blood extravasated into surrounding tissues (see also Ch. 134).

**Platelet factors:** Platelets adhere to the site of vessel wall injury and form aggregates--called hemostatic plugs--which are key to the hemostatic seal. Platelets also release factors to augment vasoconstriction (eg, serotonin, thromboxane A<sub>2</sub>) and initiate vessel wall repair (platelet-derived growth factor), and they provide surface membrane sites and components for formation of enzyme/cofactor complexes in blood coagulation reactions.

Circulating platelets do not adhere to normal endothelium or to each other but do adhere to subendothelium that is exposed when the vessel's endothelial lining is broken. Platelet adhesion requires endothelial cell secretion of the protein von Willebrand factor (VWF), which is found in the vessel wall and in plasma; VWF binds during platelet adhesion to a glycoprotein receptor of the platelet surface membrane (glycoprotein Ib).

Collagen and the first thrombin formed at the injury site activate platelets. These reactions activate phospholipase C, an enzyme that hydrolyzes inositol phospholipids. Products of this reaction activate protein kinase C and increase the Ca concentration of platelet cytosol, resulting in a series of overlapping events:

**Plasma factors:** Blood coagulation reactions form a second key element of the hemostatic seal--the fibrin clot. Radiating from and anchoring the hemostatic plug, the fibrin clot adds needed bulk.

Coagulation occurs in steps: (1) Sequences of reactions in at least two pathways (the intrinsic and extrinsic pathways) activate serine protease proenzymes and form a prothrombin activator, which is a complex (of an enzyme; factor Xa; and two cofactors, factor Va and procoagulant phospholipid) on the surface of activated platelets or tissue cells. (2) The prothrombin activator cleaves prothrombin into two fragments, one of which is the enzyme thrombin. (3) Thrombin, by cleaving small peptides from the and (fibrinopeptide A and B) chains of fibrinogen, gives

rise to an altered molecule (fibrin monomer) that polymerizes to form insoluble fibrin (fibrin polymer). Thrombin also activates factor XIII, an enzyme that catalyzes formation of covalent bonds between fibrin molecules, cross-linking the molecules to form a clot resistant to dissolution.

Ca ions are needed in most thrombin-generating reactions; thus, Ca-chelating agents (eg, citrate, edetic acid) are used in vitro as anticoagulants. Several serine protease proenzymes contain residues of  $\gamma$ -carboxyglutamic acid, which has two carboxy groups attached to the  $\gamma$ -carbon of glutamic acid. The extra carboxy group creates binding sites for Ca. These proteins containing  $\gamma$ -carboxyglutamic acid residues are called vitamin K-dependent clotting factors because vitamin K is needed to attach the added carboxy group to glutamic acid. When synthesized without vitamin K, these proteins cannot normally bind Ca or function in blood coagulation.

Reactions that generate the prothrombin activator complex may be initiated in vitro by exposing plasma to a negatively charged surface (eg, glass, certain diatomaceous earth powders) or by adding tissue factor (a tissue lipoprotein) to plasma. In the former reaction, factor XII, high mol wt kininogen, prekallikrein, and factor XI react with a negatively charged surface (contact activation reactions), giving rise to factor XIa. Factor XIa then activates factor IX. A factor X activator forms as a complex of factor IXa and two cofactors, factor VIIIa and procoagulant phospholipid; procoagulant phospholipid is present on the surface of activated platelets or tissue cells.

### **Laboratory Findings**

**Screening tests** measure combined effects of factors that influence a particular phase of coagulation (eg, bleeding time). Specific assays measure the level or function of one hemostatic factor (eg, factor VIII assay). Additional tests may measure a product or effect of pathologic in vivo activation of platelets, coagulation, or fibrinolysis (eg, level of fibrin degradation products). Screening test results and knowledge of the clinical disorder guide the selection of more specific diagnostic tests.

**The bleeding time** should be assessed with a BP cuff on the upper arm inflated to 40 mm Hg, which makes hemostatic plugs hold against a back pressure. A disposable, spring-loaded bleeding time device is used to make a 6-mm  $\times$  1-mm incision on the volar aspect of the forearm. Blood is absorbed onto the edge of a piece of filter paper at 30-sec intervals until bleeding stops. By this method, the upper limit of normal bleeding time is 7.5 min. Thrombocytopenia, disorders of platelet function, and von Willebrand's disease (VWD) may prolong the bleeding time, but it is not prolonged in coagulation-phase disorders. Use of aspirin within 5 to 7 days also prolongs bleeding time.

**Partial thromboplastin time (PTT)** screens for abnormal blood coagulation reactions triggered by exposure of plasma to a negatively charged surface. Plasma is incubated for 3 min with a reagent supplying procoagulant phospholipid and a surface-active powder (eg, micronized silica). Ca is then added, and the clotting time is noted. (Because commercial reagents and instrumentation vary widely, each laboratory should determine its own normal range; 28 to 34 sec is typical.)

The PTT is sensitive to deficiencies of 30 to 40% of all clotting factors except factors VII and XIII. With rare exceptions, a normal result rules out hemophilia. Heparin prolongs the PTT, and the PTT is often used to monitor heparin therapy. A prolonged test time can also stem from a deficiency of one or more coagulation factors or from the presence of an inhibitor of a plasma clotting factor (eg, a factor VIII anticoagulant--see Coagulation Disorders

## **Hereditary Coagulation Disorders**

### **HEMOPHILIA**

Common forms of hereditary bleeding disorders caused by clotting factor deficiencies of factor VIII, IX, or XI.

**Hemophilia A** (factor VIII deficiency), which affects about 80% of hemophiliacs, and **hemophilia B** (factor IX deficiency) have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission. Specific factor assays are required to distinguish the two.

#### **Genetics**

Hemophilia may result from gene mutations: point mutations involving a single nucleotide, deletions of all or parts of the gene, and mutations affecting gene regulation. About 50% of cases of severe hemophilia A result from a major inversion of a section of the tip of the long arm of the X chromosome. Because factor VIII and factor IX genes are located on the X chromosome, hemophilia affects males almost exclusively. Daughters of hemophiliacs will be obligatory carriers, but sons will be normal. Each son of a carrier has a 50% chance of being a hemophiliac, and each daughter has a 50% chance of being a carrier. (See also Ch. 286.) Rarely, random inactivation of one of the two X chromosomes in early embryonic life will result in a carrier's having a low enough factor VIII or IX level to experience abnormal bleeding.

#### **Symptoms and Signs**

A patient with a factor VIII or IX level  $< 1\%$  of normal has severe bleeding episodes throughout life. The first episode usually occurs before age 18 mo. Minor trauma can result in extensive tissue hemorrhages and hemarthroses, which, if improperly managed, can result in crippling musculoskeletal deformities. Bleeding into the base of the tongue, causing airway compression, may be life threatening and requires prompt, vigorous replacement therapy. Even a trivial blow to the head requires replacement therapy to prevent intracranial bleeding.

Patients with factor VIII or IX levels about 5% of normal have mild hemophilia. They rarely have spontaneous hemorrhages; however, they will bleed severely (even fatally) after surgery if not managed correctly. Occasional patients have even milder hemophilia with a factor VIII or IX level in the 10 to 30% of normal range. Such patients may also bleed excessively after surgery or dental extraction.

#### **Laboratory Findings**

By measuring the factor VIII level and comparing it with the level of VWF antigen, it is often possible to determine whether a female is a true carrier of hemophilia A. Similarly, measuring the factor IX level often identifies a carrier of hemophilia B. Polymerase chain reaction analysis of DNA in the factor VIII gene

amplified from lymphocytes is available at a few specialized centers. This test allows identification of the hemophilia A carrier, either directly by recognition of a known specific genomic defect in the pedigree, or indirectly through study of restriction fragment length polymorphisms linked to the factor VIII gene. These techniques have also been applied to the diagnosis of hemophilia A by chorionic villus sampling in the 8- to 11-wk fetus (see also Chorionic Villus Sampling in Ch. 247).

Typical findings in hemophilia are a prolonged PTT, a normal PT, and a normal bleeding time.

## **DISSEMINATED INTRAVASCULAR COAGULATION**

(Consumption Coagulopathy; Defibrination Syndrome)

Abnormal generation of fibrin in the circulating blood.

Disseminated intravascular coagulation (DIC) usually results from entrance into or generation within the blood of material with tissue factor activity, initiating coagulation (see Fig. 131-1). DIC usually arises in one of four clinical circumstances: (1) Complications of obstetrics--eg, abruptio placentae, saline-induced therapeutic abortion, retained dead fetus syndrome, the initial phase of amniotic fluid embolism. Uterine material with tissue factor activity gains access to the maternal circulation. (2) Infection, particularly with gram-negative organisms. Gram-negative endotoxin causes generation of tissue factor activity on the plasma membrane of monocytes and endothelial cells. (3) Malignancy, particularly mucin-secreting adenocarcinomas of the pancreas and prostate and acute promyelocytic leukemia, in which hypergranular leukemic cells are thought to release material from their granules with tissue factor activity. (4) Shock from any cause, probably because of the generation of tissue factor activity on monocytes and endothelial cells.

### **Symptoms and Signs**

Subacute DIC may be associated with thromboembolic complications of hypercoagulability, including venous thrombosis, thrombotic vegetations on the aortic heart valve, and arterial emboli arising from such vegetations. Abnormal bleeding is uncommon.

In contrast, thrombocytopenia and depletion of plasma clotting factors of acute, massive DIC create a severe bleeding tendency that is worsened by secondary fibrinolysis; ie, large amounts of fibrin degradation products form and interfere with platelet function and normal fibrin polymerization. If secondary fibrinolysis is extensive enough to deplete plasma 2-antiplasmin, a loss of control of fibrinolysis adds to the bleeding tendency. When massive DIC is a complication of delivery or surgery that leaves raw surfaces (eg, prostatectomy), major hemorrhage results: Puncture sites of invasive procedures (eg, arterial puncture for blood gas studies) bleed persistently, ecchymoses form at sites of parenteral injections, and serious GI bleeding may occur from erosion of gastric mucosa.

Acute DIC may also cause fibrin deposition in multiple small blood vessels. If secondary fibrinolysis fails to lyse the fibrin rapidly, hemorrhagic tissue necrosis may result. The most vulnerable organ is the blood, where fibrin deposition in the

glomerular capillary bed may lead to acute renal failure. This is reversible if the necrosis is limited to the renal tubules (acute renal tubular necrosis) but irreversible if the glomeruli are also destroyed (renal cortical necrosis). Fibrin deposits may also result in mechanical damage to RBCs with hemolysis (see Thrombotic Thrombocytopenic Purpura-Hemolytic-Uremic Syndrome in Ch. 133).

Occasionally, fibrin deposited in the small vessels of the fingers and toes leads to gangrene and loss of digits and even arms and legs.

### **Laboratory Findings**

Laboratory findings vary with the intensity of the disorder. In subacute DIC, the findings are thrombocytopenia, a normal to minimally prolonged prothrombin time (PT), a short partial thromboplastin time (PTT), a normal or moderately reduced fibrinogen level, and an increased level of fibrin degradation products. (Because illness stimulates increased fibrinogen synthesis, a fibrinogen level in the lower range of normal [eg, 175 mg/dL] is abnormal in a sick patient and raises the possibility of impaired production resulting from liver disease or increased consumption from DIC.)

Acute, massive DIC produces a striking constellation of laboratory abnormalities: thrombocytopenia; a very small clot (sometimes not even visible), noted when blood is allowed to clot in a glass tube; a markedly prolonged PT and PTT (the plasma contains insufficient fibrinogen to trigger the end point of coagulation instruments, and test results are often reported as more than some value [eg, > 200 sec], which is the interval before the automated instrument shifts to the next sample in the machine); a markedly reduced plasma fibrinogen concentration; a positive plasma protamine paracoagulation test for fibrin monomer; and a very high level of plasma D-dimer and fibrin degradation products in the serum.

Specific clotting factor assays will reveal low levels of multiple clotting factors, particularly factors V and VIII, which are inactivated because activated protein C is generated during DIC.

Massive hepatic necrosis can produce laboratory abnormalities resembling acute DIC. The factor VIII level is elevated in hepatic necrosis because factor VIII is an acute-phase protein that is made in hepatocytes and in cells in the spleen and blood; it is reduced in DIC.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. The primary factor that regulates erythropoietic activity is
    - (A) the blood
    - ( B ) erythropoietin
    - (C) the erythroid colony-forming unit (CFU-E) (D) oxygen
    - ( E ) bone marrow
  
  2. Which of the following anemias is most likely to respond to the administration of erythropoietin?
    - (A) Iron deficiency anemia (B) Pernicious anemia (C) Sideroblastic anemia (D) Pure red cell aplasia
    - ( E ) Anemia of renal disease
  3. A 48-year-old woman with known hereditary spherocytosis who usually has a mild anemia (hemoglobin of 10 g/dl and reticulocyte count of 16%) comes to the emergency room complaining of extreme shortness of breath after having had a "bad cold" for a week. Hematologic testing reveals a hemoglobin concentration of 5 g/dl, a reticulocyte count of 1%, a white cell count of 6700/ $\mu$ l, and a platelet count of 200,000/ $\mu$ l. What is the best course of action for this patient?
    - (A) Plasmapheresis to remove autoantibody directed at erythroblasts plus supportive transfusions
    - (B) Surgical consultation for thymectomy after confirming a diagnosis of pure red cell aplasia
    - (C) Slow transfusion of packed red cells to avoid volume overload plus 1 mg/day of oral folate
    - (D) Administration of 60 mg of prednisone to suppress autoantibodies directed at erythroid precursor cells
    - ( E ) Bone marrow transplantation
- 1-D 2-E 3-C

## ANSWERS AND EXPLANATIONS

### 1. The answer is D(I C 1-2; Figure 4-1J).

The primary signal triggering erythropoiesis is a decrease in the oxygen tension (i.e., hypoxia) in the blood. Tissue oxygen tension depends on the number of circulating red cells bearing functioning hemoglobin. A "sensor" thermostat in the blood is activated by renal hypoxia to transmit a "message" to erythroid-committed precursor cells (erythroid colony-forming unit, or CFU-E) in the bone marrow. The message is the erythropoietic growth factor, erythropoietin, which the blood produces and secretes into the circulation. Erythropoietin increases proliferation and maturation of the erythroid precursors and accelerates the release of new red blood cells. More red cells, then, carry higher amounts of oxygen, which increase tissue oxygen tension, which in turn cause the blood to stop releasing erythropoietin. Thus, oxygen acts as the stimulus for starting and stopping the process and the "thermostat" for maintaining a normal level of red blood cells.

### 2. The answer is E(II A 1 b, 3 e).

The major cause of anemia in renal disease is decreased levels of erythropoietin, which is produced and secreted by the blood. Clinical studies have shown that administration of exogenous erythropoietin produces normal hemoglobin levels in patients with this form of anemia. The other causes of anemia cited are associated with elevated, not decreased, erythropoietin levels. The anemia is caused by a lack of erythroid precursor cell response to erythropoietin because of either an absence of iron for the formation of hemoglobin (in iron deficiency), an absence of vitamin B<sub>12</sub> for nuclear maturation (in pernicious anemia), a defect in porphyrin synthesis for hemoglobin production (in sideroblastic anemia), or immunologic damage to the early erythroid precursors (in pure red cell aplasia).

### 3. The answer is C(II C 1 c).

Patients with chronic hemolysis are at risk for having a transient episode of red cell aplasia, or an "aplastic crisis." The episode is characterized by an acute drop in hemoglobin because of the absence of erythroid compensation for the hemolysis, as shown by a low reticulocyte count. In most cases, the aplastic crisis occurs in association with a viral infection that is self-limited; thus, transfusion support through this period is all that is necessary. Immunosuppression is effected with corticosteroids when pure red cell aplasia is associated with an autoimmune disease; cytotoxic drugs are administered when the disorder is associated with a lymphoma. Thymectomy is indicated in cases of known or suspected thymoma and in some idiopathic cases in an attempt to remove the source of the autoantibody. Plasmapheresis is another treatment used to remove autoantibodies. Bone marrow transplantation is not indicated for pure red cell aplasia but would be used for aplastic anemia, a diagnosis that can be eliminated in this patient by her normal white cell and platelet counts.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. Iron deficiency can develop in all of the follow-3. Normal or increased bone marrow iron stores

ing clinical conditions EXCEPT are found in all of the following forms of hypochro

mic, microcytic anemia EXCEPT

(A) nontropical sprue

(B) excessive menstrual flow

(C) bacterial endocarditis

(D) occult colonic carcinoma

(E) pulmonary hemosiderosis  
arthritis

(A) anemia caused by lead intoxication

(B) sideroblastic anemia

(C) iron deficiency anemia

(D) anemia associated with rheumatoid

2. A 58-year-old woman who complains of easy fatigue and weakness is found to be mildly anemic, presenting with a hemoglobin level of 10 g/dl and ferritin of 16 ng/dl. Of the following courses of management, which one is best suited to this patient?

(A) Encourage the maintenance of a well-balanced diet and monitor the anemia

(B) Prescribe oral ferrous sulfate for 6 months to replace iron stores

(C) Prescribe sustained-release iron capsules to avoid BLOOD discomfort and help ensure patient compliance

(D) Order bone marrow studies to identify iron deficiency as the source of the anemia

(E) Order stool analysis to detect the presence of occult blood

**Directions:** Each item below contains four suggested answers, of which **one or more** is correct. Choose the answer

**A** if **1, 2, and 3** are correct

**B** if **1 and 3** are correct **C** if **2**

**and 4** are correct **D** if **4** is correct

**E** if **1, 2, 3, and 4** are correct

4. Failure of a microcytic anemia to respond to oral iron replacement may be due to

(1) presence of an inflammatory bowel condition (2) malabsorption of iron (3) continued blood loss (4) sustained-release iron preparation

5. Causes of anemia of chronic disease (ACD) include which of the following?

(1) Uncomplicated diabetes mellitus (2) Tuberculosis

(3) Hypertension

(4) Rheumatoid arthritis

1-C 4-E 2-E 5-C 3-C

## ANSWERS AND EXPLANATIONS

**1. The answer is C**(IV A 1; Table 5-21).

Iron deficiency does not develop in bacterial endocarditis. Iron stores can be depleted by nontropical sprue, excessive menstrual flow, occult colonic carcinoma, and pulmonary hemosiderosis. Bacterial endocarditis and other chronic diseases that cause anemia are characterized by the increased storage of iron in the bone marrow but poor iron reutilization. Iron stores can be depleted by three mechanisms: inadequate iron intake (as in infants who are fed an unsupplemented diet of milk), iron malabsorption (as in patients with tropical or nontropical sprue), and chronic occult blood loss (as in cases of excessive menstrual bleeding, occult BLOOD bleeding in colonic carcinoma, or increased blood loss through the respiratory tract in pulmonary hemosiderosis).

**2. The answer is E**[IV E 1 a].

The best course of action to take in the management of this woman is to order stool analysis to detect the presence of occult blood. Although it is important to replace iron stores in an iron-deficient patient, it is more important to identify and treat the underlying cause of the deficiency. This is especially true for older patients in whom iron deficiency may be the presenting sign of a more serious disorder, most commonly occult BLOOD bleeding and malignancy. Therefore, stool analysis to detect the presence of occult blood is the best course of action in the management of this 58-year-old woman. Iron replacement should also be instituted, preferably with oral ferrous sulfate, since it contains 60 mg of elemental iron in each 300 mg

tablet, is well absorbed, and is inexpensive. Administration of sustained-release forms of oral iron should not be the first choice for the management since they are not well absorbed. Bone marrow studies may be required at some point in the patient management, but they should not be used as the first step in determining the cause of the iron deficiency. Diet alone cannot supply enough iron to replace deficient stores.

**3. The answer is C [IV A, IX A 3, X B 3].**

Normal or increased bone marrow stores are not found in iron deficiency anemia. The basic defect in hypochromic, microcytic anemia is a quantitative reduction in the synthesis of hemoglobin, which ultimately results in the production of red cells with reduced hemoglobin contents. Disorders of hemoglobin synthesis may involve either the heme component or the globin component. In iron deficiency, there are insufficient marrow iron stores for optimal heme synthesis, which results in hypochromic anemia. In lead poisoning, heme synthesis is impaired by the presence of lead, which inhibits the activity of certain critical enzymes; however, iron stores in the bone marrow are abundant. Sideroblastic anemia refers to a diverse group of disorders that all have impaired heme synthesis; the ultimate result is hypochromic anemia and iron loading. Anemia of chronic diseases such as rheumatoid arthritis is associated with increased iron storage with impaired iron reutilization for heme synthesis.

**4. The answer is E (all) [IV A 3, E 5].**

A patient may not respond to iron therapy for several reasons. The presence of an underlying chronic disease is the most common cause of a patient's failure to respond to iron therapy. Patients who do not absorb iron well *may* also have a malabsorption syndrome or subtotal gastrectomy, in which an insufficient amount of gastric acid interferes with the conversion of iron from the dietary to soluble form. Oral iron therapy may not be sufficient to replace the iron lost through the continued bleeding that occurs in such conditions as hereditary telangiectasia. Sustained-release iron preparations may be prescribed to avoid the BLOOD discomfort often associated with oral iron therapy. However, not enough iron may be available in the duodenum, where absorption should occur.

**5. The answer is C (2 and 4) (VI B 1 a, b).**

Anemia of chronic disease (ACD) can be caused by both tuberculosis and rheumatoid arthritis, which are inflammatory diseases in which there are activated macrophages in the reticuloendothelial system. This activation stimulates the secretion of apolactoferrin, an iron-binding protein found in phagocytic cells, into the circulation. Apolactoferrin promotes both the removal of circulating ferritin and the formation of hemosiderin, the storage form of iron. Iron stored as hemosiderin is less accessible for the synthesis of hemoglobin in erythroid cell precursors. Patients with diabetes mellitus may be highly susceptible to infections, but there is no underlying activation of the phagocytic cells. Hypertension is also not considered an inflammatory disease, and no relationship to ACD has been

noted.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. All of the following statements are true of patients with pernicious anemia (PA) EXCEPT

2. All of the following findings are present in both folate and vitamin B<sub>12</sub> deficiencies EXCEPT

(A) macrocytic red cells

(B) peripheral neuropathy

(C) Howell-Jolly bodies and Cabot's rings in the bone marrow

(D) high levels of lactate dehydrogenase (LDH) and indirect bilirubin resulting from ineffective erythropoiesis

(E) hypersegmented neutrophils with six or seven lobes

(A)

(B) (C) (D) (E)

about 75% of PA patients exhibit anti-intrinsic factor antibodies in serum

PA is associated with another autoimmune disease called Hashimoto's thyroiditis

older vegetarians develop PA because of disuse of intrinsic factor

about 90% of patients display antibodies to gastric parietal cells

PA is a consequence of long-standing gastritis, which leads to atrophy of the secretory cells of the stomach

**Directions:** Each group of items in this section consists of lettered options followed by a set of numbered items. For each item, select the **one** lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

### Questions 3-6

For each patient with megaloblastic anemia, select the associated cause or finding.

(A) Alcoholism

(B) Subacute combined degeneration of the spinal cord

(C) Abnormal results for the three parts of the Schilling test

(D) Bilobate polymorphonuclear cells

(E) Blind loop syndrome

3. A 54-year-old white male with chronic peptic ulcers and a previous gastrectomy presents with anemia, a mean corpuscular volume (MCV) of 110 fl, a red beefy

tongue, a normal level of serum folate, a low level of serum vitamin B<sub>12</sub>, and a normal neurologic examination.

4. A 43-year-old man presents with anemia, a MCV of 101 fl, a platelet count of 70,000/ $\mu$ l, a low level of serum folate, and a normal serum level of vitamin B<sub>12</sub>.

5. A 72-year-old woman who presented to a neurologist with complaints of falling is found to have anemia, a MCV of 115 fl, a platelet count of 50,000/ $\mu$ l, a white blood cell count (WBC) of 2200/ $\mu$ l, an elevated level of serum folate, and a low serum level of vitamin B<sub>12</sub> (20 ng/L).

6. A 45-year-old woman who had multiple bowel surgeries for Crohn's disease presents with anemia, a MCV of 110 fl, a WBC of 5700/ $\mu$ l, a platelet cou

## ANSWERS AND EXPLANATIONS

### 1. The answer is C[III D 3 b].

Vegetarians do well with the oral replacement of vitamin B<sub>12</sub> and develop megaloblastic anemia as a consequence of a lack of animal-derived food in their diet and not because of abnormal intrinsic factor. Rather pernicious anemia (PA) is a consequence of chronic gastritis, which causes atrophy of the stomach secretory cells. Most PA patients display anti-intrinsic factor antibodies in serum, saliva, and gastric juice as well as antibodies to the cytoplasm of gastric parietal cells. This evidence, as well as an association with other immune disorders in these patients such as Hashimoto's thyroiditis (antibodies to thyroid tissues), points to the possibility of an autoimmune mechanism for PA.

### 2. The answer is B[III B, D 1, 2].

Both folate-deficient and vitamin B<sub>12</sub>-deficient patients exhibit macrocytic red cells, Howell-Jolly bodies and Cabot's rings in the marrow, high levels of lactate dehydrogenase (LDH) and indirect bilirubin resulting from ineffective erythropoiesis, and hypersegmented neutrophils displaying six or seven lobes. However, only vitamin B<sub>12</sub>-deficient patients develop neurologic abnormalities because vitamin B<sub>12</sub> is required in myelin metabolism.

### 3-6. The answers are 3-E (III C 1, 3, D 2 b, 3 d; Table 6-2), 4-A (III D 1 b(1), (4) (a)J, 5-B (II B 2, C, • III D 3 c), 6-C (III D 2 b (3), 3 d(4)).

A patient with megaloblastic anemia and a previous history of gastrectomy should respond positively to part II of the Schilling test. However, the development of blind loop syndrome is common in gastrectomy patients and will cause a negative response to part II. This condition should respond favorably to antibiotic administration and result in a normal part III response.

Folate deficiency in patients from Western countries who present with megaloblastic anemia is most likely due to alcoholism. Alcohol also directly suppresses bone marrow activity and may decrease the platelet counts.

In severe vitamin B<sub>12</sub> deficiency in pernicious anemia (PA), subacute combined

degeneration of the spinal cord and pancytopenia manifest as neurologic symptoms. Poor conjugation of folate allows it to escape from cells into the bloodstream, causing elevated levels of serum folate (the folate trap hypothesis).

Surgical resection of the distal part of the ileum in patients with Crohn's disease is very common. The distal ileum is the site of absorption of vitamin B<sub>12</sub>. The absorption deficit will not be corrected by the administration of antibiotics in part III of the Schilling test.

**7-10. The answers are** 7-D (fl/ D 3 d], 8-A [1] A 4, B 2 a (2); III D 2 b (1), 3 d (4) (a)J, 9-B (III D 1 b (3) (a), 3 d (4)], 10-E (III D 2 b (4), 3 d (4)].

The typical findings in a patient with pernicious anemia (PA) are a low serum level of vitamin B<sub>12</sub>, a normal or elevated level of serum folate, and a failure to absorb orally administered radiolabeled vitamin B<sub>12</sub> (an abnormal response to part I of the Schilling test) that is corrected with the addition of intrinsic factor (a normal part II response).

Patients who adhere to a strict vegetarian (vegan) diet may display a low serum level of vitamin B<sub>12</sub>, which is available only in food of animal origin, and a high level of serum folate (vegetables are a rich source of folate, and its concentration is increased by the vitamin B<sub>12</sub> deficiency). The result for part I of the Schilling test is normal since there is no abnormality associated with the absorption of oral vitamin B<sub>12</sub>.

Pregnancy can cause folate deficiency by increased utilization of the easily depleted stores. Stores of vitamin B<sub>12</sub> are much larger and not so easily depleted. The Schilling test would not be indicated in this patient and would show normal results if performed.

Infestation with the fish tapeworm (*Diphyllobothrium latum*) can cause vitamin B<sub>12</sub> deficiency as the parasite utilizes vitamin B<sub>12</sub> passing through the intestine. This condition cannot be corrected by the administration of oral antibiotics unless they are prescribed specifically to treat this infestation. Therefore, the result for part III of the Schilling test would be abnormal.

III. A 58-year-old woman who complains of easy fatigue and weakness is found to be mildly anemic, presenting with a hemoglobin level of 10 g/dl and ferritin of 16 ng/dl. Of the following courses of management, which one is best suited to this patient?

- (A) Encourage the maintenance of a well-balanced diet and monitor the anemia
- (B) Prescribe oral ferrous sulfate for 6 months to replace iron stores
- (C) Prescribe sustained-release iron capsules to avoid gastrointestinal discomfort and help ensure patient compliance
- (D) Order bone marrow studies to identify iron deficiency as the source of the anemia
- (E) Order stool analysis to detect the presence of occult blood

IV. For each set of laboratory test results listed below, select the likely associated

condition.

- (A) Strict vegetarian diet
- (B) Pregnancy
- (C) Jejunal resection
- (D) Pernicious anemia (PA)
- (E) *Diphyllobothrium latum* infestation

1. Low serum level of vitamin B<sub>12</sub>, normal or high level of serum folate, and an abnormal result for part I and a normal result for part II of the Schilling test
2. Low serum level of vitamin B<sub>12</sub>, high level of serum folate, and a normal result for part I of the Schilling test
3. Normal serum level of vitamin B<sub>12</sub>, low level of serum folate, and a normal result for part I of the Schilling test
4. Low serum level of vitamin B<sub>12</sub>, normal level of serum folate, and abnormal results for parts I, II, and III of the Schilling test

V. An 18-year-old Italian tourist visiting relatives in the United States presents to the emergency room with dark urine, headache, fatigue, and back pain. He has a history of similar episodes, and he has an uncle who has had the same symptoms. He had eaten an Italian bean dish several hours before becoming sick. His hemoglobin is 10 g/dl with a reticulocyte count of 13%, and results of the urine test are positive for occult blood. Which test should be ordered next?

- (A) Hemoglobin electrophoresis
- (B) Cholecystography for bile stones
- (C) Heinz bodies test
- (D) Ham and sugar water tests
- (E) Coombs' test

## II-2. The answers are:

Prolonged partial thromboplastin time (PTT) is the most likely finding. This patient's family history suggests an X-linked inherited bleeding disorder. Mild hemophilia A or B is a strong possibility in this patient, which would show up as a prolonged PTT caused by a deficiency of either factor VIII or factor IX. The platelet count, prothrombin time (PT), thrombin time, and bleeding time would likely be normal in this patient.

The best step to be taken next is to perform specific factor assays. In a rare patient with very mild hemophilia, factor levels are not low enough to prolong the PTT but significant bleeding occurs after surgery. Assuming that this patient's maternal grandfather had mild hemophilia, the patient's mother, then, is an obligatory carrier and the patient has a 50% chance of having hemophilia. Since it is not known whether PTT was prolonged in other family members, it is prudent to perform

factor assays before proceeding with elective surgery. Screening tests of the patient's mother would likely be normal because hemophilia carriers usually have high enough levels of the affected factor to result in normal screens. Platelet aggregation studies would not be helpful in view of the normal bleeding time and apparent X-linked inheritance pattern. A mixing study generally is performed in acquired disorders to determine if the addition of normal plasma corrects an abnormal screening test and, therefore, is not helpful if the screening test is already normal.

## **II. The answer is B.**

This patient presents with the typical features of thrombotic thrombocytopenic purpura (TTP), a rare clinical syndrome that occurs most often in young women. Patients experience an acute onset of thrombocytopenia, microangiopathic hemolytic anemia, and fluctuating neurologic abnormalities, often accompanied by fever and renal dysfunction. Disseminated intravascular coagulation (DIC) is an unlikely diagnosis, given the normal prothrombin time (PT) and partial thromboplastin time (PTT) and the absence of a precipitating cause. There is no drug history; therefore, drug-induced thrombocytopenia is an unlikely explanation for the microangiopathic changes seen on peripheral blood smear. Leukemia is unlikely with a normal white cell differential. Red cell morphology should be normal in idiopathic thrombocytopenic purpura (ITP).

## **III. 2. The answer is E [IV E 1 a].**

The best course of action to take in the management of this woman is to order stool analysis to detect the presence of occult blood. Although it is important to replace iron stores in an iron-deficient patient, more important to identify and treat the underlying cause of the deficiency. This is especially true for old, patients in whom iron deficiency may be the presenting sign of a more serious disorder, most common occult gastrointestinal bleeding and malignancy. Therefore, stool analysis to detect the presence of occult, blood is the best course of action in the management of this 58-year-old woman. Iron replacement should also be instituted, preferably with oral ferrous sulfate, since it contains 60 mg of elemental iron in each - 300 mg tablet, is well absorbed, and is inexpensive. Administration of sustained-release forms of oral iron should not be the first choice for the management since they are not well absorbed. Bone marrow studies may be required at some point in the patient management, but they should not be used as the first step in determining the cause of the iron deficiency. Diet alone cannot supply enough iron to replace deficient stores.

## **IV. 7-10. The answers are 1-D, 2-A 39-B 4-E**

The typical findings in a patient with pernicious anemia (PA) are a low serum level of vitamin B<sub>12</sub>, a normal or elevated level of serum folate, and a failure to absorb orally administered radiolabeled vitamin B<sub>12</sub> (an abnormal response to part I of the Schilling test) that is corrected with the addition of intrinsic factor (a normal part II response).

Patients who adhere to a strict vegetarian (vegan) diet may display a low serum level of vitamin B<sub>12</sub>, which is available only in food of animal origin, and a high

level of serum folate (vegetables are a rich source of folate, and its concentration is increased by the vitamin B<sub>12</sub> deficiency). The result for part I of the Schilling test is normal since there is no abnormality associated with the absorption of oral vitamin B<sub>12</sub>.

Pregnancy can cause folate deficiency by increased utilization of the easily depleted stores. Stores of vitamin B<sub>12</sub> are much larger and not so easily depleted. The Schilling test would not be indicated in this patient and would show normal results if performed.

Infestation with the fish tapeworm (*Diphyllobothrium latum*) can cause vitamin B<sub>12</sub> deficiency as the parasite utilizes vitamin B<sub>12</sub> passing through the intestine. This condition cannot be corrected by the administration of oral antibiotics unless they are prescribed specifically to treat this infestation. Therefore, the result for part III of the Schilling test would be abnormal.

## V. The answer is C

Symptoms as occurred in the Italian tourist suggest a diagnosis of glucose-6-phosphate dehydrogenase

(G6PD) deficiency of the Mediterranean type (class II). An enzyme deficiency of less than 10% results in

episodic symptoms brought about by the ingestion of an oxidative agent found in fava beans, which causes denaturation and precipitation of the patient's hemoglobin and is shown in the Heinz bodies test. Class I (< 5%) G6PD deficiency is severe, with chronic hemolysis; it is called congenital non spherocytic hemolytic anemia. Measurement of the level of G6PD in the red cells in the class III variant is not helpful since the enzyme levels increase with reticulocytosis; in the severe class I and class II forms, the enzyme levels are not elevated in the reticulocytes and would remain low during the hemolytic process.

## Approach to Patients with Immune System, Connective Tissue and Joints Diseases

*Immunodeficiency diseases: A group of diverse conditions caused by one or more immune system defects and characterized clinically by increased susceptibility to infections with consequent severe, acute, recurrent, or chronic disease.*

An immunodeficiency disorder should be considered in anyone with infections that are unusually frequent, severe, and resistant; without a symptom-free interval; from an unusual organism; or with unexpected or severe complications. Since immunodeficiency disorders are relatively uncommon, other disorders leading to recurrent infection should be considered first. If these disorders can be excluded, a defect in host defense should be suspected.

### Primary And Secondary Immunodeficiencies

Immunodeficiencies may be primary or secondary. **Primary immunodeficiency** is classified into four main groups depending on which component of the immune system is deficient: B cells, T cells, phagocytic cells, or complement. (An overview of immune system components is given in Ch. 146.) Over 70 primary immunodeficiencies have been described, and considerable heterogeneity may exist within each disorder. A classification of the primary deficiencies is shown in Table 147-2 (unusual variants are excluded).

T-cell defects include several disorders with associated B-cell (antibody) defects, which is understandable since B and T cells originate from a common primitive stem cell and T cells influence B-cell function. Phagocytic diseases include disorders in which the primary defect is one of cell movement (chemotaxis) and those in which the primary defect is one of microbicidal activity.

Of the primary immunodeficiencies, B-cell or antibody defects predominate; selective IgA deficiency (usually asymptomatic) may occur in 1/400 people. Excluding asymptomatic IgA deficiency, B-cell defects account for 50% of the primary immunodeficiencies; T-cell deficiencies, about 30%; phagocytic deficiencies, 18%; and complement deficiencies, 2%. The overall incidence of *symptomatic* primary immunodeficiency is estimated to be 1/10,000; about 400 new cases occur each year in the USA. Since many primary immunodeficiencies are hereditary or congenital, they appear initially in infants and children; about 80% of those affected are < 20 yr old and, owing to

X-linked inheritance of many syndromes, 70% occur in males.

**Secondary immunodeficiency** is an impairment of the immune system resulting from an illness in a previously normal person. The impairment often is reversible if the underlying condition or illness resolves. Secondary immunodeficiencies are considerably more common than primary immunodeficiencies and occur in many hospitalized patients. Nearly every prolonged serious illness interferes with the immune system to some degree. A classification of the secondary immunodeficiencies is shown in Table 147-3.

## **Etiology**

Immunodeficiency has no common cause, although a single gene defect is often implicated. The defect can lead to a missing enzyme (eg, adenosine deaminase deficiency), a missing protein (eg, complement component deficiencies), or developmental arrest at a specific differential stage (eg, pre-B-cell arrest in X-linked agammaglobulinemia). Chromosome locations of the defective genes have been identified for many of the primary immunodeficiencies. In certain illnesses, intrauterine events may be implicated (eg, maternal alcoholism in some cases of DiGeorge anomaly); in others, drug ingestion may be implicated (eg, phenytoin in IgA deficiency). The exact biologic abnormality in most of the illnesses is unknown.

## **Symptoms and Signs**

Most manifestations of immunodeficiency result from frequent infections, usually beginning with recurrent respiratory infections. (However, many immunologically normal infants have six to eight respiratory infections per year, particularly when exposed to older siblings or other children.) Further, most immunodeficient patients eventually develop one or more severe bacterial infections that persist, recur, or lead to complications; eg, sinusitis, chronic otitis, and bronchitis often follow repeated episodes of sore throat or URI. Bronchitis may progress to pneumonia, bronchiectasis, and respiratory failure, the most common cause of death. Infections with opportunistic organisms (eg, *Pneumocystis carinii* or cytomegalovirus) may occur, particularly in patients with T-cell deficiencies.

Infection of the skin and mucous membranes also is common. Resistant thrush may be the first sign of T-cell immunodeficiency. Oral ulcers and periodontitis also are noted, particularly in granulocytic deficiencies. Conjunctivitis occurs in many antibody-deficient adults. Pyoderma, severe warts, alopecia, eczema, and telangiectasia are common.

Common symptoms include diarrhea, malabsorption, and failure to thrive. The diarrhea usually is noninfectious but may be associated with *Giardia lamblia*, rotavirus, cytomegalovirus, or *Cryptosporidium*. In some patients, the diarrhea

may be exudative with loss of serum proteins and lymphocytes.

Less common manifestations of immunodeficiency include hematologic abnormalities (autoimmune hemolytic anemia, leukopenia, thrombocytopenia), autoimmune phenomena (vasculitis, arthritis, endocrinopathies), and CNS problems (eg, chronic encephalitis, slow development, seizures).

## Diagnosis

A family history should be obtained. If there is a history of early death, similar disease, autoimmune illness, allergy, early malignancy, or consanguinity, then a pedigree chart will help identify a hereditary pattern. A history of adverse reactions to immunizations or viral infections should be noted as well as prior surgery (eg, splenectomy, tonsillectomy, adenoidectomy); radiation therapy to the thymus or nasopharynx; and prior antibiotic and immune globulin (IG) therapies and their apparent clinical benefit.

**The type of infection** may suggest the nature of the immunodeficiency. Infections with major gram-positive organisms (pneumococci, streptococci) are noted in antibody (B-cell) immunodeficiencies. Severe infections from viruses, fungi, and other opportunistic organisms are common in cellular (T-cell) immunodeficiencies. Recurrent staphylococcal and gram-negative infections are common in phagocytic deficiencies. Recurrent *Neisseria* infection is characteristic in patients with several complement component deficiencies. Certain opportunistic infections (eg, from *P. carinii*, *Cryptosporidium*, or *Toxoplasma*) may occur in several types of immunodeficiency.

**The age of onset** also may help in diagnosis; infants < 6 mo old usually have a T-cell defect. However, onset of illness around 6 mo of age, when transplacentally acquired maternal antibodies have disappeared, suggests congenital antibody deficiency.

On **physical examination**, patients with immunodeficiency often appear chronically ill, with pallor, malaise, malnutrition, and a distended abdomen. Macular rashes, vesicles, pyoderma, eczema, petechiae, alopecia, or telangiectasia may appear on the skin. Conjunctivitis is common, particularly in adults. Cervical lymph nodes and adenoid and tonsillar tissue typically are absent in B- or T-cell immunodeficiency, despite a history of recurrent throat infections. This can be confirmed by a lateral pharyngeal x-ray, which may show absence of adenoidal tissue. Occasionally, the lymph nodes are enlarged and suppurative. The tympanic membranes often are scarred or perforated. The nostrils may be excoriated and crusted, indicative of purulent nasal discharge. Postnasal drip and a decreased gag reflex may be present. Often there is a chronic cough. Rales are often present, especially in adults with

immunodeficiency. The liver and spleen frequently are enlarged. Muscle mass and fat deposits of the buttocks are diminished. In infants, there may be excoriation around the anus as a result of chronic diarrhea. Neurologic examination may reveal delayed developmental milestones or ataxia.

## Laboratory Tests

In all cases of immunodeficiency, selected tests are needed to confirm or establish the diagnosis; advanced tests often are necessary to subclassify the disorder required for rational therapy (see [Table 147-5](#)). Screening tests can be performed in most offices and hospitals and advanced tests in most large hospitals, but specialized tests are available only in laboratories or in hospitals with a sophisticated immunology laboratory.

When immunodeficiency is suspected, the screening tests recommended include a CBC with differential and platelet count; determination of IgG, IgM, and IgA levels; assessment of antibody function; and clinical and laboratory evaluation of the infection.

The CBC will establish the presence of anemia, thrombocytopenia, neutropenia, or leukocytosis. The total lymphocyte count should be noted; lymphopenia ( $< 1500/\mu\text{L}$ ) is suggestive of T-cell immunodeficiency. The peripheral smear should be examined for the presence of Howell-Jolly bodies and other unusual RBC forms suggestive of asplenia or poor splenic function. The granulocytes may show morphologic abnormalities (eg, granules of the Chédiak-Higashi syndrome).

**Tests for B-cell (antibody) deficiency:** If Ig levels are very low (total  $< 200$  mg/dL), a diagnosis of antibody deficiency is established, and other procedures are indicated only to define the exact illness and identify other immunologic defects. If Ig levels and preexisting antibody titers are low but not absent, the antibody responses to one or more standardized antigens should be assessed. Antibody titers are obtained before and 3 to 4 wk after immunization with tetanus toxoid or *H. influenzae* type B vaccines (for protein antigen responsiveness) or after immunization with pneumococcal or meningococcal vaccine (for polysaccharide antigen responsiveness). An inadequate response (less than a fourfold rise in titer) is suggestive of antibody deficiency regardless of Ig levels.

**Tests for T-cell deficiency:** Profound and prolonged lymphopenia suggests a T-cell immunodeficiency; however, lymphopenia is not always present. A chest x-ray is a useful screening test in an infant; an absent thymic shadow in the newborn period suggests T-cell deficiency, particularly if the x-ray is obtained before the onset of infection or other stress that may shrink the thymus.

Delayed hypersensitivity skin tests are valuable screening tests after the age of 2 yr. The following antigens are used: mumps, *Candida* (1:100), fluid tetanus toxoid (1:10), and *Trichophyton*. Nearly all adults and most immunized infants and children will react to one or more of these antigens with erythema and induration ( $> 5$  mm) at 48 h. The presence of one or more positive delayed skin test results generally suggests an intact T-cell system.

The most valuable advanced test in cellular immunodeficiency is T-cell and T-subset (helper/inducer and suppressor/cytotoxic) enumeration, usually performed by flow cytometry using T-cell-specific monoclonal murine antibodies. Total T cells are measured using a pan T-cell antibody (eg, anti-CD3, anti-CD2); T-helper/inducer cells are measured using an anti-CD4 antibody; and suppressor/cytotoxic cells are measured using an anti-CD8 antibody. (Such assays have in general replaced sheep-cell rosetting techniques to enumerate T cells.) A T-helper cell (CD4) count  $< 500$  cells/ $\mu$ L is highly suggestive of a T-cell immunodeficiency, and a CD4 count  $< 200$  cells/ $\mu$ L indicates a profound T-cell immunodeficiency. The ratio of CD4/CD8 (helper/suppressor) cells should be  $> 1.0$ ; reversal of this ratio also suggests T-cell immunodeficiency (eg, in AIDS, a decline in the CD4/CD8 ratio indicates progressive immunologic impairment). Monoclonal antibodies also are available to identify activated cells (CD25), natural killer cells (CD16 and CD56), and immature T-cell (thymocyte) antigens (CD1).

Another useful advanced test measures the ability of the patient's lymphocytes to proliferate and enlarge (transform) when cultured in the presence of mitogens (eg, phytohemagglutinin, concanavalin A), irradiated allogeneic WBCs (in the mixed leukocyte reaction), or antigens to which the patient has been previously exposed. Under these stimuli, normal lymphocytes undergo rapid division, which can be assessed morphologically or by uptake of radioactive thymidine into dividing cells. Proliferation usually is reported as an index--the ratio of counts/min of stimulated cells to counts/min of an equal number of unstimulated cells. Patients with T-cell immunodeficiency have low or absent proliferative responses in proportion to the degree of immune impairment. The proliferative responses to mitogens (which activate all cells) are considerably higher (stimulation index, 50 to 100) than the response to antigens or allogeneic cells (stimulation index, 3 to 30).

Special tests also assess lymphokine production after mitogen or antigen stimulation. Although  $> 30$  lymphokines exist, interferon- $\gamma$ , interleukin-2, interleukin-4, and tumor necrosis factor- $\alpha$  are most often assayed. Certain patients have adequate proliferative responses but deficient lymphokine production (eg, migration inhibition factor deficiency in chronic mucocutaneous candidiasis). Other tests assess cytotoxic function. Different types of cytotoxicity (natural killer, antibody-dependent, or cytotoxic T cell) are measured using different tumor cell or virus-infected target cells.

Cytotoxic defects are variably present in cellular immunodeficiency. In some forms of combined immunodeficiency, enzymes of the purine pathway (adenosine deaminase, nucleoside phosphorylase) are deficient and can be assayed with RBCs. Levels of various thymic hormones (thymosin, facteur thymique serique) can be assessed; these are low in certain cellular immunodeficiencies. HLA typing can be valuable for assessing the presence of two populations of cells (chimerism) and for excluding deficiencies of HLA antigens (bare lymphocyte syndrome).

**.Tests for phagocytic cell deficiency:** An investigation is indicated when a patient with a convincing history of immunodeficiency has normal B- and T-cell immunity. A lack of pus formation at the site of inflammation and delayed umbilical cord detachment with marked leukocytosis are clues suggestive of a chemotactic defect.

In addition to the blood count, initial screening should include an IgE level, which is elevated in many chemotactic disorders, and a nitroblue tetrazolium (NBT) dye reduction test for chronic granulomatous disease, the most common phagocytic disorder. The NBT test is based on the increased metabolic activity of granulocytes during phagocytosis and killing with reduction of colorless NBT to blue formazan. This color change, absent in chronic granulomatous disease, can be assessed visually, microscopically, or by spectrophotometry.

Next, phagocytosis is tested by measuring uptake of latex particles or bacteria by isolated granulocytes or monocytes. Microbial killing is then assessed by mixing the patient's granulocytes in fresh serum with a known number of live bacteria, followed by serial quantitative bacterial assays over a 2-h period.

Other specialized tests define phagocytic defects: assays of granulocyte mobilization after administering corticosteroids, epinephrine, or endotoxin; quantitative assays of granulocyte enzymes (myeloperoxidase, G6PD, etc); assays for granulocyte oxidant products (hydrogen peroxide, superoxide); and assays for specific granulocyte proteins (CR3 [CD11] adhesive glycoproteins, nicotinamide adenine dinucleotide phosphate oxidase components). The latter can distinguish the four genetic types of chronic granulomatous disease.

**Tests for complement deficiency:** A complement abnormality is screened by measuring the total serum complement activity ( $\text{CH}_{50}$ ) and serum C3 and C4 levels. Low levels of any of these should be followed by titration of the classic and alternative complement pathways and the measurement of individual complement components. Deficiency of classic pathway components is also associated with immunologic renal disease, serum sickness reactions, or acute infections. Monospecific antisera or sensitized RBCs and solutions that contain all components except for the one to be assessed are used to measure

complement components.

## **Hypersensitivity**

Hypersensitivity refers to pathologic processes that result from immunologically specific interactions between antigens (exogenous or endogenous) and humoral antibodies or sensitized lymphocytes. This definition excludes those disorders in which demonstrated antibodies have no known pathophysiologic significance (eg, the antibody to heart tissue that follows heart surgery or MI), even though their presence may have diagnostic value.

Any classification of hypersensitivity will be oversimplified. Some are based on the time required for symptoms or skin test reactions to appear after exposure to an antigen (eg, immediate and delayed hypersensitivity), on the type of antigen (eg, drug reactions), or on the nature of organ involvement. Moreover, classifications do not take into account that more than one type of immune response may be occurring or that more than one type may be necessary to produce immunologic injury.

### **The Gell and Coombs Classification**

This classification of reactions, consisting of four types, is widely used despite limitations, because it is the most satisfactory.

**Type I** are reactions in which antigens (allergens) combine with specific IgE antibodies that are bound to membrane receptors on tissue mast cells and blood basophils. The antigen-antibody reaction causes the rapid release of potent vasoactive and inflammatory mediators, which may be preformed (eg, histamine, tryptase) or newly generated from membrane lipids (eg, the leukotrienes and prostaglandins). Over hours, mast cells and basophils also release proinflammatory cytokines (eg, interleukin-4 and interleukin-13). The mediators produce vasodilation, increased capillary permeability, glandular hypersecretion, smooth muscle spasm, and tissue infiltration with eosinophils and other inflammatory cells.

**Type II** are cytotoxic reactions resulting when antibody reacts with antigenic components of a cell or tissue elements or with antigen or hapten that is

coupled to a cell or tissue.

The antigen-antibody reaction may activate certain cytotoxic cells (killer T cells or macrophages) to produce antibody-dependent cell-mediated cytotoxicity. It usually involves complement activation and may cause opsonic adherence through coating of the cell with antibody; the reaction develops by activation of complement components through C3 (with consequent phagocytosis of the cell), or by activation of the full complement system with consequent cytolysis or tissue damage.

**Type III** are immune complex (IC) reactions resulting from deposition of soluble circulating antigen-antibody ICs in vessels or tissue. The ICs activate complement and thus initiate a sequence of events that results in polymorphonuclear cell migration and release of lysosomal proteolytic enzymes and permeability factors in tissues, thereby producing acute inflammation. Consequences of IC formation depend in part on the relative proportions of antigen and antibody in the IC. With an excess of antibody, the ICs rapidly precipitate where the antigen is located (eg, within the joints in RA) or are phagocytosed by macrophages and thus do no harm. With a slight excess of antigen, the ICs tend to be more soluble and may cause systemic reactions by being deposited in various tissues.

**Type IV** are cellular, cell-mediated, delayed, or tuberculin-type hypersensitivity reactions caused by sensitized T lymphocytes after contact with a specific antigen.

Circulating antibodies are not involved in nor are they necessary for development of tissue injury. Transfer of delayed hypersensitivity from sensitized to nonsensitized persons can occur with peripheral lymphocytes, but not with serum.

Sensitized T lymphocytes that are triggered or activated by contact with a specific antigen may cause immunologic injury by a direct toxic effect or through the release of soluble substances (lymphokines). In tissue culture, activated T lymphocytes destroy target cells after sensitization by direct contact. Cytokines released from activated T lymphocytes include several factors that affect the activity of macrophages, neutrophils, and lymphoid killer cells (see [Table 146-1](#)).

## Disorders With Type I Hypersensitivity Reactions

Disorders included with type I hypersensitivity reactions are the **atopic diseases (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and allergic [extrinsic] asthma [see Ch. 68]) and some cases of urticaria and GI food reactions and systemic anaphylaxis.**

The incidence of **asthma** has increased markedly, although the causes are largely unknown. Recently, a marked increase in type I reactions has been noted in relation to exposure to water-soluble proteins in **latex products** (eg, rubber gloves, dental dams, condoms, tubing for respiratory equipment, catheters, and enema tips with inflatable latex cuffs), particularly among medical personnel and patients exposed to latex and children with spina bifida and urogenital birth defects. Common reactions to latex are **urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, and anaphylaxis.**

**History:** Review of the symptoms, their relation to the environment and to seasonal and situational variations, their clinical course, and the family history of similar problems should yield sufficient information to classify the disease as atopic. The history is more valuable than tests in determining whether a patient is allergic, and the patient should not be subjected to extensive skin testing unless reasonable clinical evidence of atopy exists. Age of onset may be an important clue (eg, childhood asthma is more likely to be allergy-related than is asthma beginning after age 30). Also indicative are seasonal symptoms (eg, correlating with specific pollen seasons) or symptoms that appear after exposure to animals, hay, or dust, or that develop in specific environments (eg, at home). The effects of contributory factors (eg, tobacco smoke and other pollutants, cold air, exercise, alcohol, certain drugs, and life stresses) should be evaluated.

**Nonspecific tests:** Eosinophils in the blood and secretions are often associated with atopic disease, particularly asthma and atopic dermatitis. IgE levels are elevated and will rise during exacerbations and fall during remissions in atopic dermatitis. Although usually elevated, IgE levels are not diagnostically useful in atopic asthma and allergic rhinitis. Occasionally, very high IgE levels may help confirm the diagnosis of allergic pulmonary aspergillosis (see Ch. 76) or hyper-IgE syndrome (see Ch. 147).

**Specific tests:** Specific tests are used to confirm sensitivity to a particular allergen or allergens. Skin tests are the most convenient way to confirm specific sensitivity. They should be selective and based on clues provided by the history. Test solutions are made from extracts of inhaled, ingested, or injected materials (eg, wind-borne tree, grass, and weed pollens; house dust mites; animal danders and sera; insect venoms; foods; and penicillin and its derivatives). Until recently, few allergen extracts were standardized and their potency was highly variable. Many commonly used extracts are now standardized.

For the prick (puncture) test, which is usually performed first, a drop of a dilute allergenic extract is placed on the skin, which is then pricked or punctured through

the extract, usually by "tenting" up the skin with the tip of a stylet or #27 needle held at a 20° angle until the tip pops loose.

For the intradermal test, just enough dilute sterile extract is injected (using a 0.5- or 1-mL syringe and a #27 short-bevel needle) to produce a 1- or 2-mm bleb. Each set of skin tests should include the diluent alone as a negative control and histamine (10 mg/mL of the base for the prick test or 0.1 mg/mL for the intradermal test) as a positive control. A skin test is considered positive if it produces a wheal and flare reaction in 15 min with a wheal diameter at least 5 mm larger than the control.

The prick skin test is usually sufficient for detecting sensitivity to most allergens.

The more sensitive intradermal test can then be used to test suspected inhaled allergens that have produced negative or equivocal prick tests. For foods, prick tests alone are diagnostic. Intradermal tests to food are likely to produce positive reactions of no clinical significance, as determined by double-blind, oral symptom-provoking challenge tests.

A radioallergosorbent test (RAST) may be performed when direct skin testing is impossible because of generalized dermatitis, extreme dermatographia, or the patient's inability to cooperate or to stop using antihistamines. A RAST detects the presence of allergen-specific serum IgE. A known allergen, in the form of an insoluble polymer-allergen conjugate, is mixed with the serum to be tested. Any IgE in the serum that is specific for the allergen will attach to the conjugate. The quantity of allergen-specific IgE in the patient's circulation is determined by adding 125I-labeled anti-IgE antibody and measuring the amount of radioactivity taken up by the conjugate.

WBC histamine release, an in vitro test, detects allergen-specific IgE on sensitized basophils by measuring allergen-induced histamine release from the patient's WBCs. This valuable research tool has given insight into the mechanisms of the allergic response; like RAST, it provides no additional diagnostic information and is seldom, if ever, used clinically.

Provocative challenge may be performed when a positive skin test raises a question about the role of the particular allergen in the production of symptoms. The allergen may be applied to the eyes, nose, or lungs. Ophthalmic testing offers no advantage over skin testing and is rarely used. Nasal challenge, performed occasionally, is primarily a research tool. Bronchial challenge, also primarily a research tool, is sometimes used when the clinical significance of a positive skin test is unclear or when skin test reagents are unavailable to show that symptoms are related to materials to which a patient is exposed (eg, in occupation-related asthma). Oral provocative challenges must be used when regularly occurring symptoms are suspected of being food-related because positive skin tests are not necessarily clinically significant. A negative skin test with a reliable antigen preparation does, however, rule out the possibility of clinical symptoms to that food. Provocative challenge is the only way to test food additives. (See below for elimination diets and challenge testing.)

Tests of unproven effectiveness: No evidence supports the use of cutaneous or sublingual provocation testing or leukocytotoxic testing in allergy diagnosis.

## **ATOPIC DISEASES**

### **Allergic Rhinitis**

IgE-mediated rhinitis, characterized by seasonal or perennial sneezing, rhinorrhea, nasal congestion, pruritus, and, often, conjunctivitis and pharyngitis.

### **HAY FEVER**

#### **(Pollinosis)**

The acute seasonal form of allergic rhinitis.

Hay fever is generally induced by wind-borne pollens. The spring type is due to tree pollens (eg, oak, elm, maple, alder, birch, juniper, olive); the summer type, to grass pollens (eg, Bermuda, timothy, sweet vernal, orchard, Johnson) and to weed pollens (eg, Russian thistle, English plantain); and the fall type, to weed pollens (eg, ragweed). Occasionally, hay fever is caused primarily by airborne fungal spores. Important geographic regional differences occur.

#### **Symptoms and Signs**

The nose, roof of the mouth, pharynx, and eyes begin to itch gradually or abruptly after the pollen season begins. Lacrimation, sneezing, and clear, watery nasal discharge accompany or soon follow the pruritus. Frontal headaches and irritability may occur. More rarely, anorexia, depression, and insomnia may occur. The conjunctiva is injected, and the nasal mucous membranes are swollen and bluish red. Coughing and asthmatic wheezing may develop as the season progresses.

#### **Diagnosis**

The history indicates the nature of the allergic process and often the pollens responsible. Diagnosis is supported by the physical findings and eosinophils in the nasal secretions. Skin tests are useful to confirm or identify the responsible pollens.

### **PERENNIAL RHINITIS**

Nonseasonal rhinitis, which may or may not be allergic, sometimes complicated by sinusitis, nasal polyps, or sensitivity to aspirin and other NSAIDs.

#### **Symptoms, Signs, and Diagnosis**

In contrast to hay fever, symptoms of perennial rhinitis vary in severity (often unpredictably) throughout the year. Extranasal symptoms (eg, conjunctivitis) are uncommon, but chronic nasal obstruction is often prominent and may extend to the eustachian tube. The resultant hearing difficulty is particularly common in children. The diagnosis is supported by a positive history of atopic disease, the characteristic bluish red mucosa, numerous eosinophils in the nasal secretions, and positive skin tests (particularly to house dust mites, cockroaches, animal danders, or fungi). Some patients have complicating sinus infections and nasal polyps.

Differential diagnosis: Some patients with negative skin tests and numerous eosinophils in their nasal secretions suffer from chronic rhinitis, sinusitis, and polyps, called eosinophilic nonallergic rhinitis or nonallergic rhinitis with eosinophilia. These patients are not atopic, but often have sensitivity to aspirin and other NSAIDs; a subset of patients suffer only from chronic rhinitis.

Some patients suffer from vasomotor rhinitis, which is characterized by mild but annoying chronic continuous nasal obstruction or rhinorrhea and no demonstrable allergy, polyps, infection, eosinophilia, or drug sensitivity (see Ch. 86). An

additional group of patients suffer rhinitis from the overuse of topical ( -adrenergic) decongestants (rhinitis medicamentosa).

### **Allergic Conjunctivitis**

Allergic inflammation of the conjunctiva.

Allergic conjunctivitis of an acute or chronic catarrhal form is usually part of a larger allergic syndrome (eg, hay fever), but it may occur alone through direct contact with airborne substances (eg, pollen, fungal spores, dusts, animal danders). (See also Vernal Keratoconjunctivitis in Ch. 95.)

Symptoms, Signs, and Diagnosis

Prominent itching may be accompanied by excessive lacrimation. The conjunctiva is edematous and hyperemic. The cause is often suggested by the patient's history and may be confirmed by skin testing.

### **Other Allergic Eye Diseases**

The lids may be involved by angioedema or urticaria, contact dermatitis, or atopic dermatitis. Contact dermatitis of the eyelids, a cellular (delayed, type IV) hypersensitivity reaction, may be caused by various ophthalmic drugs or others conveyed by the fingers to the eyes (eg, antibiotics by drug handlers) or by face powder, nail polish, or hair dye. The cornea may become involved by extension of allergic conjunctivitis or by a variant of superficial punctate keratitis, leading rarely to scarring.

Pain, photophobia, lacrimation, and circumcorneal ciliary inflammation indicate probable anterior uveitis. The cause is usually unknown. Sympathetic ophthalmia is believed to be a hypersensitivity reaction to uveal pigment. Endophthalmitis phacoanaphylactica is allergy to native lens protein. This severe reaction to remaining lens material occurs typically hours after uneventful cataract extraction, although it may follow trauma or inflammation involving the lens capsule. Prompt evaluation and treatment by an ophthalmologist are required in these serious conditions (see also Ch. 98).

### **Food Allergy and Intolerance**

Food allergy is reproducible symptoms occurring after ingestion of a specific food and for which an immunologic basis (IgE antibodies to the food) is proved. Food intolerance involves clinical GI reactions in which the mechanism is not immunologic or is not known.

Many common (probably psychophysiologic) adverse food reactions are attributed to food allergy when no convincing cause-and-effect evidence exists, at least of the type of allergy that can be evaluated by skin tests and is associated with specific IgE antibodies to foods. Certain claims are controversial and almost surely untrue; eg, that intolerance (or allergy) to food or food additives can be responsible for hyperactive children, the tension-fatigue syndrome, and enuresis. Unsubstantiated claims blame food allergy for arthritis, obesity, suboptimal athletic performance, and depression, among other conditions.

Occasionally, cheilitis, aphthae, pylorospasm, spastic constipation, pruritus ani, and perianal eczema have been attributed to food allergy or intolerance, but the association is difficult to prove. Recently, food intolerance was found to be

responsible for symptoms of some patients with the irritable bowel syndrome, confirmed by double-blind food challenge. An increase in rectal prostaglandin levels was noted when a reaction occurred. Preliminary information suggests that the same phenomenon may take place occasionally in patients with chronic ulcerative colitis.

**Eosinophilic enteropathy**, which may be related to specific food allergy, is an unusual illness involving pain, cramps, and diarrhea associated with blood eosinophilia, eosinophilic infiltrates in the gut, protein-losing enteropathy, and a history of atopic disease. Rarely, dysphagia occurs, indicating esophageal involvement.

True IgE-mediated food allergy usually develops in infancy, most often in those with a strong family history of atopy.

#### Symptoms and Signs

The first manifestation may be eczema (atopic dermatitis) alone or in association with GI symptoms. By the end of the first year, dermatitis usually has lessened and allergic respiratory symptoms may develop. Asthma and allergic rhinitis can be aggravated by allergy to foods that can be identified by skin testing. However, as the child grows, foods become less important, and he reacts increasingly to inhaled allergens. By the time the child with asthma and hay fever is 10 yr old, it is rare for a food to provoke respiratory symptoms, even though positive skin tests persist. If atopic dermatitis persists or appears in the older child or adult, its activity seems to be largely independent of IgE-mediated allergy, even though atopic patients with extensive dermatitis have much higher IgE levels in the serum than those who are free of dermatitis.

Most young food-allergic patients are sensitive to potent allergens (eg, allergens in eggs, milk, peanuts, and soy). Older people may react violently to ingesting even a trace of such foods and other foods (especially shellfish), experiencing explosive urticaria, angioedema, and even anaphylaxis. Anaphylaxis may occur in patients with a lower level of sensitivity only if they exercise after eating the offending food.

**Milk intolerance** is sometimes caused by an intestinal disaccharidase deficiency and is expressed by GI symptoms (see also Carbohydrate Intolerance in Ch. 30). In other patients, milk causes GI and even respiratory symptoms for no known reason. Food additives can produce systemic symptoms (monosodium glutamate); asthma (metabisulfite, tartrazine--a yellow dye); and possibly urticaria (tartrazine). These reactions are not caused by IgE antibodies. A few patients suffer from food-induced or aggravated migraine, confirmed by blinded oral challenge.

Digestion effectively prevents food allergy symptoms in most adults. This is illustrated by allergic patients who react on inhalation or contact but not on ingestion of an allergen (eg, in baker's asthma, the affected workers wheeze on exposure to flour dust and have positive skin tests to wheat and/or other grains, yet have no problem eating grain products).

#### Diagnosis

Severe food allergy is usually obvious in adults. When it is not, or in most children, diagnosis may be difficult and the condition must be differentiated from functional GI problems.

In persons suspected of having reactions to foods after eating, the relationship of symptoms to foods is first tested by appropriate skin tests. A positive test does not prove clinically relevant allergy, but a negative test rules it out. With a positive skin test, clinically relevant sensitivity can be determined by an elimination diet and, if symptoms improve, by reexposure to the food to determine if it can induce symptoms. All positive challenges should be followed by a double-blind challenge to be considered definitive. The basic diet is determined by eliminating foods suspected by the patient of causing symptoms or by prescribing a diet composed of relatively nonallergenic foods (see Table 148-3).

Foods that commonly cause allergy are milk, eggs, shellfish, nuts, wheat, peanuts, soybeans, and all products containing one or more of these ingredients. Most common allergens and all suspected foods must be eliminated from the starting diet. No foods or fluids may be consumed other than those specified in the starting diet. Eating in restaurants is not advisable, since the patient (and physician) must know the exact composition of all meals. Pure products must always be used; eg, ordinary rye bread contains some wheat flour.

If no improvement occurs after 1 wk, another diet should be tried. If symptoms are relieved, one new food is added and more than the usual amount is eaten for > 24 h or until symptoms recur. Alternatively, small amounts of the food to be tested are eaten in the physician's presence, and the patient's reactions observed. Aggravation or recrudescence of symptoms after the addition of a new food is the best evidence of allergy. Such evidence should be verified by noting the effect of removing that food from the diet for several days, then restoring it.

## **ANAPHYLAXIS**

An acute, often explosive, IgE-mediated systemic reaction that occurs in a previously sensitized person who receives the sensitizing antigen.

Anaphylaxis occurs when antigen (proteins, polysaccharides, or haptens coupled with a carrier protein) reaches the circulation. The most common causative antigens are parenteral enzymes, blood products, -lactam antibiotics and many other drugs, allergen immunotherapy (desensitization), and insect stings. -blockers, even as eyedrops, may aggravate anaphylactic reactions. Anaphylaxis can be aggravated or even induced de novo by exercise, and some patients have recurrent symptoms for no identifiable reason. Histamine, leukotrienes, and other mediators are generated or released when the antigen reacts with IgE on basophils and mast cells. These mediators cause the smooth muscle contraction (responsible for wheezing and GI symptoms) and vascular dilation that characterize anaphylaxis. Vasodilation and escape of plasma into the tissues causes urticaria and angioedema and results in a decrease in effective plasma volume, which is the major cause of shock. Fluid escapes into the lung alveoli and may produce pulmonary edema. Obstructive angioedema of the upper airway may also occur. Arrhythmias and cardiogenic shock may develop if the reaction is prolonged.

Anaphylactoid reactions are clinically similar to anaphylaxis, but may occur after the first injection of certain drugs (polymyxin, pentamidine, opioids) and contrast media. They have a dose-related, toxic-idiosyncratic mechanism rather than an immunologically mediated one. Aspirin and other NSAIDs can cause reactions in susceptible patients.

### **Symptoms and Signs**

Symptoms vary, and rarely does any one patient develop all the symptoms. Typically, in 1 to 15 min (but rarely after as long as 2 h), the patient feels uneasy, becomes agitated and flushed, and complains of palpitations, paresthesias, pruritus, throbbing in the ears, coughing, sneezing, urticaria and angioedema, and difficulty breathing owing to laryngeal edema or bronchospasm. Nausea, vomiting, abdominal pain, and diarrhea are less common. Shock may develop within another 1 or 2 min, and the patient may convulse, become incontinent, become unresponsive, and die. Primary cardiovascular collapse can occur without respiratory symptoms. Recurrent episodes of anaphylaxis in the same person are usually characterized by the same symptoms.

### **DISORDERS OF VASOACTIVE MEDIATORS**

Disorders with manifestations of vasoactive mediators derived from mast cells and other sources (even though an IgE-mediated or other immunologic mechanism may not be involved).

#### **Urticaria and Angioedema**

(Hives; Giant Urticaria; Angioneurotic Edema)

Urticaria is local wheals and erythema in the superficial dermis. Angioedema is a deeper swelling due to edematous areas in the deep dermis and subcutaneous tissue and may also involve mucous membranes.

#### **Etiology**

Acute urticaria and angioedema are essentially anaphylaxis limited to the skin and subcutaneous tissues and can be due to drug allergy, insect stings or bites, desensitization injections, or ingestion of certain foods (particularly eggs, shellfish, or nuts). Some reactions occur explosively after ingestion of minute amounts.

Others (eg, reactions to strawberries) may occur only after overindulgence and possibly result from direct (toxic) mediator liberation. Urticaria may accompany or even be the first symptom of several viral infections, including hepatitis, infectious mononucleosis, and rubella. Some acute reactions are unexplained, even when recurrent. If acute angioedema is recurrent, progressive, painful rather than pruritic, and not associated with urticaria, a hereditary enzyme deficiency should be considered (see Hereditary Angioedema, below).

Chronic urticaria and angioedema lasting > 6 wk are more difficult to explain, and only in exceptional cases can a specific cause be found. The reactions are rarely IgE-mediated. Occasionally, chronic ingestion of an unsuspected drug or chemical is responsible; eg, from penicillin in milk; from the use of nonprescription drugs; or from preservatives or other food additives. Chronic underlying disease (SLE, polycythemia vera, lymphoma, or infection) should be ruled out. Though often

suspected, controllable psychogenic factors are rarely identified. Urticaria caused by physical agents is discussed under Physical Allergy, below. A few patients with intractable urticaria have thyroid disease. Occasionally, urticaria may be the first or only visible sign of cutaneous vasculitis.

### Symptoms and Signs

In urticaria, pruritus (generally the first symptom) is followed shortly by the appearance of wheals that may remain small (1 to 5 mm) or enlarge (see Plate 148-1). The larger ones tend to be clear in the center and may be noticed first as large rings (> 20 cm across) of erythema and edema. Ordinarily, crops of hives appear and subside; a lesion may remain in one site for several hours, then disappear, only to reappear elsewhere. If a lesion persists  $\geq$  24 h, the possibility of vasculitis should be considered.

Angioedema is characterized by a more diffuse and painful swelling of loose subcutaneous tissue, dorsum of hands or feet, eyelids, lips, genitalia, and mucous membranes. Edema of the upper airways may produce respiratory distress, and the stridor may be mistaken for asthma.

### Diagnosis

The cause of acute urticaria or acute angioedema is usually obvious. Even when it is not, diagnostic tests are seldom required because of the self-limited, nonrecurrent nature of these reactions. In chronic urticaria, an underlying chronic disease should be ruled out by a detailed history and physical examination and routine screening tests. Eosinophilia is uncommon in urticaria. Other tests (eg, stool examination for ova and parasites, serum complement, antinuclear antibody, and sinus or dental x-rays) are not helpful without additional clinical indications.

## Disorders With Type II Hypersensitivity Reactions

### Diagnosis

Tests to support this mechanism of immunologic injury include detecting the presence of antibody or complement on the cell or on tissue or detecting the presence, in serum, of antibody to a cell surface antigen, a tissue antigen, a receptor, or a foreign (exogenous) antigen. Although complement often is required for type II cell injury and may be detected on the cell or in the tissue, total serum hemolytic complement activity is not depressed, as often occurs in immune complex (IC) hypersensitivity reactions (type III; see below).

The direct antiglobulin (Coombs') and anti-non- -globulin tests detect antibody and complement on RBCs, respectively. These tests use rabbit antisera, one to immunoglobulin (Ig) and the other to complement. When these reagents are mixed with RBCs coated with Ig or complement, agglutination occurs. Antibodies eluted from these cells show both a specificity for RBC blood group antigens and an ability to fix complement, thus showing that they are true autoantibodies and account for the complement present on the RBCs in the direct non- -globulin test. The indirect antiglobulin test detects the presence of a circulating antibody to RBC antigens. The patient's serum is incubated with RBCs of the same blood group (to preclude false results due to incompatibility); the antiglobulin test is then

performed on these RBCs. Agglutination confirms the presence of circulating antibody to RBC antigens.

In penicillin-induced hemolytic anemia, the patient has a positive direct Coombs' test while receiving penicillin but has a negative indirect antiglobulin test using RBCs of the same type as the patient. The patient's serum, however, will agglutinate the indirect-test RBCs if they are coated with penicillin.

Fluorescence microscopy is most commonly used to detect Ig or complement in tissue (by the direct technique) and also can be used to determine the specificity of a circulating antibody (by the indirect technique). In the direct immunofluorescence technique, animal antibody specific for human Ig or complement is labeled with a fluorescent dye (usually fluorescein) and then layered on tissue. When the tissue is examined under the fluorescence microscope, a typical fluorescent color (green for fluorescein) indicates the presence of human Ig or complement in the tissue. Direct immunofluorescence also can be used to detect other serum proteins, tissue components, or exogenous antigen as long as specific animal antibodies to them can be produced. The technique itself does not indicate a cell-specific antigen unless the antibody can be eluted from the tissue and its specificity for tissue antigens determined.

In Goodpasture's syndrome, the immunofluorescence pattern is seen as a linear fluorescence on kidney and lung basement membrane. When antibody is eluted from the kidney of a patient with Goodpasture's syndrome and layered on normal kidney or lung, it attaches to the basement membrane and gives the same linear fluorescence pattern when tested with fluorescein-labeled antibody to human  $\gamma$ -globulin (indirect immunofluorescence).

In pemphigus, the direct immunofluorescence technique reveals antibody to an antigen in the intercellular cement of the prickle cell layer; in pemphigoid, to an antigen in the basement membrane. In both diseases, serum antibody is detectable by the indirect immunofluorescence technique. This immunofluorescence technique is used to detect tissue-specific circulating antibodies in many other disorders; eg, antithyroid antibodies in thyroiditis and antinuclear and anticytoplasmic antibodies in SLE.

Antireceptor tests to detect antibody to the acetylcholine receptors are commercially available, but tests for the insulin and thyroid receptors are not.

There are no clinical situations in which the antibody-dependent cytotoxicity test is necessary. See also Autoimmune Disorders, below.

## **Disorders With Type III Hypersensitivity Reactions**

### **Diagnosis**

Type III reactions can be suspected in human disease when vasculitis occurs. In polyarteritis, the presence of vasculitis is the only clinical evidence to support a role for ICs. Further support may be obtained by direct immunofluorescence tests (as described above), which may indicate the presence of antigen, immunoglobulin (Ig), and complement in the area of vasculitis.

In experimental studies, fluorescence microscopy shows a coarse granular deposit (lumpy bumps) along the basement membrane when animal glomeruli are stained for Ig and complement. A similar distribution can be seen in type III human renal diseases (see Ch. 231). The electron microscope also can be used to detect electron-dense deposits (similar to those seen in experimental serum sickness), which are believed to be the antigen-antibody complexes. Rarely, both antigen and antibody can be detected by immunofluorescence in the inflamed tissue--this has been shown in the renal disease of SLE and in the vasculitic lesions of hepatitis-antigen-associated serum sickness.

A type III reaction is further evidenced by demonstrating the presence of circulating antibody to antigen, such as horse serum, hepatitis antigen, DNA, altered IgG (rheumatoid factor), and some molds. In SLE, for example, a rise in antibody to native undenatured, double-stranded DNA and a fall in serum complement occur during exacerbations of renal disease. If the antigen is unknown, levels of total serum complement and of the early components (C1, C4, or C2) can be tested; a depressed level indicates classic complement activation and, therefore, a type III reaction.

In allergic pulmonary aspergillosis, an intradermal skin test with *Aspergillus* antigen may produce an IgE-mediated wheal and flare reaction followed by an Arthus-like reaction.

Until recently, ICs were detected in serum by cryoprecipitation (using the property of some complexes to precipitate in the cold). Sophisticated equipment also could detect soluble complexes by analytic ultracentrifugation and sucrose density gradient centrifugation. Currently, several tests detecting circulating ICs are used based on the ability of complexes to react with complement components (eg, C1q-binding assays) and the ability of complexes to inhibit the reaction between monoclonal rheumatoid factor and IgG. Assays such as the Raji cell assay are based on the interaction of ICs containing complement components with cellular receptors (eg, a C3 receptor on the Raji cell). Although others are available, such assays are used most commonly. No single test detects all ICs, and their use in clinical medicine is limited to monitoring the activity of certain diseases.

## **AUTOIMMUNE DISORDERS**

Disorders in which the immune system produces autoantibodies to an endogenous antigen, with consequent injury to tissues.

### **Pathogenesis**

The pathogenetic mechanisms of autoimmune reactions are, in many cases, better understood than the way in which autoantibodies develop. In some autoimmune

hemolytic anemias, the RBCs become coated with cytotoxic (type II) autoantibody; the complement system responds to these antibody-coated cells just as it does to similarly coated foreign particles, and the interaction of complement with the antibody complexed to the cell surface antigen leads to RBC phagocytosis or cytolysis.

Autoimmune renal injury can occur as the result of either an antibody-mediated (type II) or IC (type III) reaction. The antibody-mediated reaction occurs in Goodpasture's syndrome, in which lung and renal disease is associated with an anti-basement membrane antibody (see Ch. 77). The best known example of autoimmune injury associated with soluble antigen-antibody complexes (ICs) is the nephritis associated with SLE (see Systemic Lupus Erythematosus in Ch. 50 and below). Another example is a form of membranous glomerulonephritis that is associated with an IC containing renal tubular antigen. Although not proven, poststreptococcal glomerulonephritis could be due in part to streptococcus-induced cross-reacting antibodies.

Various autoantibodies are produced in SLE and other systemic (as opposed to organ-specific) autoimmune diseases. Antibodies to formed elements in the blood account for autoimmune hemolytic anemia (see Ch. 127), thrombocytopenia, and possibly leukopenia; anticoagulant antibodies may cause disordered coagulation problems. Antibodies to nuclear material result in deposition of ICs, not only in glomeruli but also in vascular tissues and in skin at the dermal-epidermal junction. Synovial deposition of aggregated IgG-rheumatoid factor-complement complexes occurs in RA. Rheumatoid factor is usually an IgM (occasionally IgG or IgA) with specificity for a receptor on the constant region of the heavy chain of autologous IgG. The IgG-rheumatoid factor-complement aggregates can also be found within neutrophils, where they cause the release of lysosomal enzymes that contribute to the inflammatory joint reaction. Many plasma cells are present within the joint and may synthesize anti-IgG antibodies. T cells and lymphokines are also found in rheumatoid joints and may contribute to the inflammatory process. The process that sets off the immunologic events is unknown; it could be a bacterial or viral infection. In SLE, the low serum complement level reflects the widespread immunologic reactions taking place; in RA, by contrast, serum complement is normal but intrasynovial complement levels are low.

In pernicious anemia, autoantibodies capable of neutralizing intrinsic factor are found in the GI lumen. Autoantibodies against the microsomal fraction of gastric mucosal cells are even more common. It is postulated that a cell-mediated autoimmune attack against the parietal cells results in the atrophic gastritis, which, in turn, reduces the production of intrinsic factor but still allows absorption of sufficient vitamin B12 to prevent the megaloblastic anemia. If autoantibodies to intrinsic factor should also develop in the GI lumen, however, B12 absorption would cease and pernicious anemia would develop.

Hashimoto's thyroiditis is associated with autoantibodies to thyroglobulin, the microsomes of thyroid epithelial cells, a thyroid cell surface antigen, and a second colloid antigen. Tissue injury and eventual myxedema may be mediated both by the cytotoxicity of the microsomal antibody and by the activity of specifically

committed T cells. Low-titered antibodies are also found in patients with primary myxedema, suggesting that it is the end result of unrecognized autoimmune thyroiditis. An autoimmune reaction is also involved in thyrotoxicosis (Graves' disease), and about 10% of patients eventually develop myxedema spontaneously; many more do so after ablative therapy. Other antibodies unique to Graves' disease are called thyroid-stimulating antibodies. They react with thyroid-stimulating hormone (TSH) receptors in the gland and have the same effect as TSH on thyroid cell function.

### **Disorders With Type IV Hypersensitivity Reactions**

Some clinical conditions in which type IV reactions are believed to be important are contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, some forms of drug sensitivity, thyroiditis, and encephalomyelitis after rabies vaccination. Evidence for the last two is based on experimental models, and in human disease on the appearance of lymphocytes in the inflammatory exudate of the thyroid and brain.

#### **Diagnosis**

A type IV reaction can be suspected when an inflammatory reaction is characterized histologically by perivascular lymphocytes and macrophages. Delayed hypersensitivity skin tests (see discussion of tests for T-cell deficiency in Ch. 147) and patch tests are the most readily available methods of testing for delayed hypersensitivity.

To prevent exacerbation of contact dermatitis, patch tests are performed after the contact dermatitis has cleared. The suspected allergen (in appropriate concentration) is applied to the skin under a nonabsorbent adhesive patch and left for 48 h. If burning or itching develops earlier, the patch is removed. A positive test consists of erythema with some induration and, occasionally, vesicle formation. Because some reactions do not appear until after the patches are removed, the sites are reinspected at 72 and 96 h.

### **HYPERSENSITIVITY TO DRUGS**

Drug eruptions are discussed in Ch. 118. Discussed here are other hypersensitivity reactions that can follow oral or parenteral drug administration. Contact dermatitis, which is a cellular (delayed, type IV) hypersensitivity reaction that follows topical use, is discussed in Ch. 111; drug reactions that result from nonimmunologic mechanisms are discussed in allergic reactions to components in donor blood, see. Before attributing a given reaction to a drug, it should be noted that placebos also may cause a wide variety of symptoms and even objective signs, such as skin rashes. Nevertheless, true drug reactions constitute a major medical problem. The

literature on specific drugs should be consulted for the most likely adverse reactions.

With a drug overdosage, toxic effects occur in direct relation to the total amount of drug in the body and can occur in any patient if the dose is large enough. Absolute overdosage results from an error in the amount or frequency of individual doses.

Relative overdosage may be seen in patients who, because of liver or kidney disease, do not metabolize or excrete the drug normally.

In drug intolerance, the adverse reaction develops on the first use of the drug. It may be the same toxic reaction ordinarily expected at higher doses, or it may be an exaggeration of a common mild side effect (eg, antihistaminic sedation).

Idiosyncrasy is a condition in which the adverse reaction on first use of the drug is pharmacologically unexpected and unique.

Tests to practicum: “Allergic and immune system disorder patients examination“

**Which from the stated below assertions, concepts, and clinical situations are associated only with the allergic reactions:**

- A. I type
- B. II and the III type
- C. IV type
- D. all types
- E. are not the allergic reactions

1. In 15 minutes after introduction of novocaine for anaesthetizing of extraction of tooth patients blood pressure fell down to 60/0 mm Hg.
2. In three days after setting of chloramphenicol to the patient with festering paradontite in the blood test absent eosinophils, basophils, band neutrophils and sharply diminished segmented neutrophils. Necrotic quinsy began.
3. The Mantu Reaction
4. Post streptococcal glomerulonephritis
5. Hay fever
6. Urticaria
7. The Gregersen Reaction
8. Bronchial asthma
9. sharp rhinitis in 5 minutes after the contact with pollen of plants

10. Heavy defeat of mucus shell of mouth cavity after chewing of pill of antibiotic

**Which from the stated below disorders gave to do to one of systems below:**

- A. Skin, sub derma and mucus shells
- B. Cardio-vascular system
- C. Alimentary tract and kidney
- D. Respiratory tract
- E. Hematology

11. Hay fever
12. Anaphylaxis
13. Glomerulonephritis
14. Bronchial asthma
15. Sharp diffuse myocarditis
16. Sharp rhinitis
17. Gingivitis
18. Autoimmune hemolytic anemia
19. Medicament's agranulocytosis
20. Angioedema
21. Allergic vasculites
22. Stomatitis
23. Ulcerous colitis

3. Answer ( C ) –reaction of sensibilisate lymphocytes
4. Answer (B)– immunocomplex disease
5. Answer (A) – pollinosis – IgE reaction
6. Answer (D)– pollinosis – IgE reaction
7. Answer (E) – Gregersen reaction light bloody stool
8. Answer (D)- all type reaction
9. Answer (A) - pollinosis – IgE reaction
10. Answer (D) - pollinosis – IgE reaction
11. Answer (A) - mucus
12. Answer (B) - collaps
13. Answer (C) -kidney
14. Answer (D) –respiratory tract
15. Answer ( B ) -myocordites
16. Answer (A) - mucus
17. Answer (A) - mucus
18. Answer (E) - blood
19. Answer (E) -blood
20. Answer (A) - subcutaneous
21. Answer (B) –vascular
22. Answer (A) - mucus
23. Answer (C) – alimentary tract

## Answers and explanations

1. Answer (A) collaps by anaphylaxis.
2. Answer (B) –reaction antigen-antibody on surface of blood cells

## Comprehensive exam

### STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the one lettered answer or completion that is best in each case.

1. A 49-year-old, previously healthy but overweight, male, bank executive comes in with the CC: "I have a cough." He admits to smoking two packs of cigarettes a day. The man claims to be happily married and lives in Simsbury with his wife and two children. He is not taking any medication. Which of the following best illustrates the identifying data?

- (A) A 49-year-old bank executive who smokes two packs of cigarettes a day presents with the CC: "I have a cough"  
 (B) A 49-year-old black bank executive presents with the

CC: "I have a cough"

(C) A 49-year-old previously healthy bank executive presents with the CC: "I have a cough"

(D) A 49-year-old smoker from Simsbury presents with the CC: "I have a cough"

(E) A 49-year-old happily married man with two children presents with the CC: "I have a cough"

2. A 70-year-old retired baker has a broken leg, hypertension, heartburn, IDDM, myopia, decreased hearing, and COPD. The HPI should include how many of these problems?

(A) 3 (B) 4 (C)

5 (D) 6 (E) 7

3. A 54-year-old electrician comes in with the CC: "I have carpal tunnel syndrome." The best response is to find out

(A) when the carpal tunnel syndrome began

(B) the chronology of the carpal tunnel syndrome

(C) what symptoms the patient has

(D) how the carpal tunnel syndrome has affected the ADLs

(E) if this is the first episode

4. All of the following are components of the HPI EXCEPT

(A) recurrences

(B) changeover time

(C) effects on the ADLs

(D) etiology of symptom

(E) location

5. Vague words that should be clarified by the clinician while taking the medical history include all of the following EXCEPT

(A) tired ( B ) dizzy

(C) hiccups (D) sick, ( E ) socially

6. While taking a PMH, the clinician learns that a patient is taking digoxin, a cardiac medication. The clinician should

(A) list the digoxin in the PMH

(B) find out about the cardiac symptom and put it in the PMH

(C) find out how long the patient has been taking the digoxin

(D) find out about the cardiac symptom and put it in the ROS

(E) find out about the cardiac symptom and put it in the HPI

7. In a PP, the category that best differentiates patients

with cancer is

(A) primary site of cancer

(B) place of employment

(C) number of children

(D) response to disease

(E) type of treatment

8. For an 85-year-old woman, all of the following components of the PMH are crucial EXCEPT

(A) allergies

(B) childhood history

(C) medication

(D) surgical history

(E) alcohol use history

9. All of the positive findings listed below belong in the ROS of a 65-year-old man EXCEPT

(A) occasional chest pains

(B) occasional headaches

(C) occasional knee stiffness

(D) hay fever

(E) decreased hearing

### Questions 11-15

Each description of pain that follows, select the **part** of the HPI in which it belongs. (A) Chronology

(B) Quantity

(C) Aggravating factors

(D) Setting

(E) Quality

11. The pain starts when doing aerobics

12. The pain lasts for 10 minutes

13. The pain is like a dull, achy pressure

14. The pain occurs nightly, two or three times a week for the past 3 weeks

15. The pain increases if the patient does not stop aerobics

## ANSWERS AND EXPLANATIONS

**1. The answer is A.** Identifying data should be short, succinct sentences with a name, age, sex, occupation, and occasionally any pertinent medical information that will help in hearing or reading the HPI. In the case presented in the question, the smoking history is related to the CC of cough. Ethnicity is not an issue with this CC and should not be included. Although marital and living status are appropriate to the PP, they are not essential to the identifying data.

**2. The answer is B.** Fractured leg, hypertension, IDDM, and COPD are all active problems. Although it is safe to assume that the fractured leg is the acute problem, the three chronic problems need monitoring and treatment. The myopia, decreased hearing, and heartburn are important to note in the ROS, but unless there is some acute pain or exacerbation, they do not need the seven parameters to be explored.

**3. The answer is C.** The clinician should not accept tertiary information. Before obtaining the seven parameters of a symptom, the clinician must clarify and verify that the syndrome or disease stated in the CC is true. Without this knowledge, the clinician may miss a diagnosis and prescribe incorrect treatment.

**4. The answer is D.** The etiology of a symptom is not information that is sought from patients for inclusion in the HPI. The etiology is hypothesis-verified by the history, physical examination, and laboratory results. The seven parameters of each symptom reported by the patient, including recurrences, changes over time, effects of the ADLs, and location, are necessary to complete the HPI.

**5. The answer is C.** Vague words often have different meanings for different people. These words must be clarified so that the clinician and patient know exactly what is meant. Hiccups is the only nonambiguous word listed and does not need clarification.

**6. The answer E.** Any problem or symptom for which patients are currently being treated should be included in the HPI and have the seven parameters determined. Digoxin is a cardiac medication that cannot be forgotten and put in the PMH. Any cardiac symptom needs to be uncovered and reported in the HPI.

**7. The answer is D.** A patient's response to illness is so varied that this information helps to personalize two people with the same diagnosis. The primary site of cancer and its treatment are important medical facts that are not relevant to the PP. The number of children and place of employment are part of the PP, but without more information, these facts do not give great insight.

**8. The answer is B.** Although childhood illnesses are part of the PMH, they are less relevant for an 85-year-old woman. Rarely can 85-year-old individuals remember when and

what they had as a child. If a major disease has continued through adulthood, then this will be ascertained during the adult PMH. The patient's surgical history as well as medications, alcohol, and allergies are essential in treating the patient now.

**9. The answer is A.** Occasional headache, knee stiffness, hay fever, and decreased hearing are fairly common maladies that occur in a 65-year-old man. Occasional chest pain, which may signal a cardiac problem, needs more clarification, including exploration by the seven parameters. Unless the clinician believes that the chest pain is totally benign, it should be discussed in the HPI.

**11-15. The answers are: 11-D, 12-A, 13-E, 14-A, 15-C.** The setting is the background in which a problem occurs. In this case, the pain begins while the patient does aerobics, which gives the clinician valuable information.

The length of time a symptom lasts is part of the chronology of a symptom. The chronology also includes previous episodes, duration, and any change in pattern. A pain that occurs nightly, two or three times a week for the past 3 weeks describes the chronology of the symptom.

The quality of a symptom is a description of the characteristics of the symptom. Descriptive words, such as dull, achy pressure, help to differentiate the pain. The quantity of a symptom rates the magnitude of the pain. Aggravating factors are conditions that cause the symptom to continue to get worse. In this case, the aerobics (exercise), which increases the pain, is an aggravating factor.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. The patient should be in a seated position for which of the following components of the examination?

- (A) Auscultation of the heart with the bell of the stethoscope
- (B) Examination of the male genitalia
- (C) Inspection of the female breast
- (D) Palpation of the abdomen
- (E) Percussion of the abdomen

2. A patient is brought to the emergency room in January after being found comatose in a snow bank. An electronic thermometer records a rectal temperature of 94° F. Which of the following statements about this patient's temperature is true?

- (A) An oral thermometer would measure core body temperature more accurately
- (B) A mercury thermometer would be less accurate than an electronic thermometer
- (C) The temperature should be confirmed with an oral temperature reading
- (D) The true temperature may actually be above 94° F
- (E) A special probe should be used in cases of potential

hypothermia

3. A 75-year-old man presents for a complete physical examination. Detailed inspection of the skin includes a description of all of the following EXCEPT

- (A) skin color
- (B) hair distribution
- (C) skin turgor
- (D) skin lesions
- ( E ) abnormal pigmentation

4. All of the following statements are true regarding the thyroid examination EXCEPT

- (A) a gland that is palpable is abnormal
- (B) the preferred position is for the examiner to reach both hands around the neck with the fingers forward
- (C) upon swallowing, the gland should slide upward
- (D) a vascular hum heard with the stethoscope implies hyperactivity of the gland
- ( E ) a normal gland may be visible by inspection

5. An 18-year-old patient with a long history of asthma presents to an emergency room in marked respiratory distress. All of the following physical findings are likely to be present EXCEPT

- (A) the diaphragm moves upward with inspiration
- (B) the respiratory rate is 16
- (C) the patient uses the trapezius muscles on inspiration
- (D) intercostal muscle retractions are noted
- (E) the patient is cyanotic

6. A patient presents with a history of an irregular heart beat. All of the following procedures are correct EXCEPT

- (A) the radial pulse should be palpated for 30 seconds
- (B) the stethoscope should be used to auscultate on the apex of the heart
- (C) the radial pulse rate should be contrasted to the apical heart rate
- (D) the carotid pulse can be palpated and used to replace the radial pulse
- (E) a complete cardiac examination should be performed

7. All of the following findings support venous disease in the lower extremities EXCEPT

- (A) pale cool extremities bilaterally
- ( B ) a deep purple color
- (C) bilateral edema to the knees
- (D) bilateral tibia) ulcers
- ( E ) a palpable cord in the right popliteal fossa

8. In what order should the abdominal examination sequence proceed?

- (A) Inspection, auscultation, palpation, percussion (B) Inspection, palpation, auscultation, percussion (C) Inspection, palpation, percussion, auscultation (D) Inspection, percussion, auscultation, palpation (E) Palpation, auscultation, inspection, percussion.

9. The effectiveness of the spleen examination is improved by all of the following factors EXCEPT

- (A) a thin patient
- (B) asking the patient to take slow deep breaths
- (C) advancing the examiner's fingers on expiration
- (D) asking the patient to roll on the left lateral decubitus
- ( E ) asking the patient to place his or her left hand under the left buttocks

10. Tests of cerebellar function include all the following EXCEPT

- (A) rapid alternating movements
- ( B ) finger-to-nose
- (C) heel-to-chin
- (D) Romberg reflex
- ( E ) deep tendon reflexes

11. A 30-year-old asymptomatic woman presents for a routine physical examination. A comprehensive periodic health evaluation for this patient should include all of the following EXCEPT

- (A) a blood pressure recording (B) a complete breast examination (C) a pelvic examination and Pap smear (D) a flexible sigmoidoscopy (E) counseling on smoking and alcohol use

## ANSWERS AND EXPLANATIONS

**1. The answer is C.** The breast examination begins in the seated position to inspect for symmetry and retractions. The bell of the stethoscope is used to listen for an  $S_3$ ,  $S_4$ , and a mitral stenosis murmur. All of these are best done in the supine or left lateral decubitus position. The male genital examination should be done in the standing position to detect hernias. The entire abdominal examination is done in the supine position to decrease muscle tone and maximize access to the abdominal contents.

**2. The answer is E.** Electronic or mercury thermometers are equally effective in measuring temperature, but the preferred method of measuring core body temperature is a rectal thermometer. The limitation of an electronic thermometer is that it does not record temperatures below 94° F. Therefore, a special probe must be used in cases of suspected hypothermia as the true temperature of the patient described in the question may be below 94° F.

**3. The answer is C.** Skin turgor is determined by palpation. Turgor is determined by gently compressing the skin between the thumb and forefinger and releasing. Skin color, hair distribution, abnormal pigmentation and the presence or absence of skin lesions are all determined by inspection.

**4. The answer is A.** A normal gland may be visible and sometimes palpable, especially in thin patients. The preferred position for examination is with the examiner in the back or on the side of the patient. Normal glands should slide upward upon swallowing. In hyperthyroidism, a vascular hum can be heard, implying increased vascular blood flow.

**5. The answer is B.** A young patient in respiratory distress should have a respiratory rate far higher than 16. All other physical symptoms described are consistent with someone in respiratory distress. Trapezius and intercostal muscles are recruited to aid respiration when the patient has a respiratory compromise. Cyanosis is a physical sign, indicating lack of oxygenation.

**6. The answer is A.** Patients with an irregularly irregular heart beat require a thorough cardiovascular evaluation, including a complete cardiac examination. Either the radial pulse or the carotid pulse can be palpated for a minimum of 60 seconds. This should be contrasted to the apical heart rate as heard by auscultation with the stethoscope, since some arrhythmias present with a pulse deficit as recorded peripherally.

**7. The answer is A.** Pale cool extremities suggest arterial insufficiency. Venous insufficiency presents with edema, a violaceous hue, and in severe cases, with skin ulceration. A deep venous thrombosis is suggested by a palpable cord in the popliteal area.

**8. The answer is A.** A careful detailed inspection should be the first component of every examination. The examination sequence for the abdominal examination differs from that of the chest or cardiac examination. Auscultation must come before palpation and percussion. Palpation and percussion may alter bowel sounds (i.e., decrease or increase their intensity). Auscultating first gives a more accurate representation of true bowel sounds.

**9. The answer is D.** Even normal spleens may be palpable in a thin patient. The technique of the examination is to have the patient take slow deep breaths and advancing fingers on expiration. The spleen becomes easier to palpate if the patient rolls to the right lateral decubitus position or places his or her left hand under the left buttock.

**10. The answer is E.** Careful examination of cerebellar function includes testing arms, legs, and gait. Rapid alternating movements and finger-to-nose both test upper extremity coordination. Heel-to-chin measures lower extremity cerebellar function. Romberg reflex and gait test overall cerebellar function. Deep tendon

reflexes do not test cerebellar functions.

**11. The answer is D.** The purpose of a comprehensive periodic health examination is to detect asymptomatic diseases for which the patient is at high risk as well as providing an opportunity for health risk identification and counseling. Blood pressure recording is recommended for all age-groups. A menstruating female should have a yearly breast examination and a biannual pelvic examination and Pap smear. Counseling on health risk, such as smoking and alcohol use, are crucial. While the recommendation for flexible sigmoidoscopy is controversial, the asymptomatic patients should not begin routine sigmoidoscopies until age 40 or 50.

**DIRECTIONS:** Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

1. A patient with low-grade fever and weight loss has poor excursion on the right side of the chest, with decreased fremitus, flatness to percussion, and decreased breath sounds all on the right. The trachea is deviated to the left. Likely diagnosis is

- a. Pneumothorax
- b. Pleural effusion
- c. Consolidated pneumonia
- d. Atelectasia

2. A 60-year-old female with a history of urinary tract infection, steroid-dependent chronic obstructive lung disease, and asthma presents with right side infiltrates and an eosinophil count of 15%. She had all findings at right side: BESIDES:

- a) RONCHI,
- b) DECREASED FREMITUS,
- c) flatness to percussion,
- d) decreased breath sounds

3. A 40-year-old alcoholic develops cough and fever. Chest xray shows an air-fluid level in the superior segment of the right lower lobe. He had all findings at right lower lobe side: BESIDES:

- a) RONCHI,
- B) INCREASED FREMITUS,
- c) flatness to percussion,
- d) decreased breath sounds

4. A 64-year-old woman is found to have a left-sided pleural effusion on chest x-ray.

Which of the following will be discovered in this patient?

- a. increased fremitus
- b. ronchi
- c. haemoptysis
- d. flatness by percussion
- e. increased breath sounds

5. A 40-year-old man without a significant past medical history comes to the emergency room with a three-day history of fever and shaking chills, with a 15-minute episode of rigor, nonproductive cough, and anorexia, as well as the development of right-sided pleuritic chest pain and shortness of breath over the last 12 hours. A chest roentgenogram reveals a consolidated right middle lobe infiltrate, and a CBC shows an elevated neutrophils count with many band forms present. Which of the following statements is correct?

- e) he has pleural effusion
- f) it is dullness by percussion on right side
- g) he hasn't pleural noise
- h) many neutrophils band forms present suggest absence of inflammation.

6. The most likely finding in a patient with acute pulmonary

embolus is all, **beside**

- a. Wheezing
- b. Pleuritic chest pain
- c. Tachypnea
- d. Haemoptysis
- e. Right-sided S<sub>3</sub> heart sound

7. A 65-year-old male with mild congestive heart failure is to receive total hip replacement. He has no other underlying diseases, no history of hypertension, recent surgery, or bleeding disorder. The best approach to prevention of pulmonary embolus in this patient is

- a. Aspirin-75 mg per day
- b. Aspirin-325 mg per day
- c. Warfarin
- d. Early ambulation

8 The hallmark of asthma that distinguishes it from other obstructive airway diseases is that in asthma:

- a. Hyperinflation is present on chest roentgenogram
- b. Airway obstruction is reversible
- c. Hypoxia occurs as a consequence of ventilation-perfusion mismatch
- d. The FEV<sub>1</sub>/FVC ratio is reduced
- e. Exacerbation often occurs as a result of an upper respiratory tract infection

9. 45-year-old man with bronchial **asthma** complains of a **productive cough** and **hemoptysis**. He also complains of progressively increasing breathlessness with intermittent attacks of severe dyspnea.

Which of following physical exam finding do **not belong** that patient?

- f) **tachypnea**
- g) clubbing of fingernails
- h) wheezes
- i) **eosinophilia**
- j) dullness to percussion

10. A 76-year-old male presents to the emergency room with **confusion** and a **severe cough**.

The patient's illness began with the **abrupt onset of headache, muscle aches, and weakness** followed 24 hours later by **high fevers and shaking chills**. He subsequently developed a **nonproductive cough with pleuritic chest pain, dyspnea, nausea, vomiting, and diarrhea**. He is a chronic **smoker** and drinks heavily. Vital Signs: **high fever** (40.0 C); **bradycardia** (HR 50); tachypnea (26 /min); normal BP. Physical Examination: disoriented; diaphoretic; **crackles bilaterally**. Cell Blood Count: **elevated WBC** (18,000). Electrolytes: **hyponatremia**. Gram stain of sputum reveals numerous neutrophils & no bacteria; **increased Legionella titers**, patchy bronchopneumonia.

Which of following physical exam finding do **not belong** that patient?

- a. bradypnea
- b. fine whizzing
- c. haemoptysis
- d. flatness by percussion
- e. increased breath sounds

## Answers and explanations

1. **The answer is b. - Pleural effusion . Pneumothorax** – *Free air between the visceral and parietal pleurae*, characterized by tympani by percussion. **Consolidated pneumonia** - characterized by increased fremitus. **Atelectasia** - *A shrunk, airless state affecting all or part of a lung*, characterized by the trachea and heart are deviated toward the affected side.
2. **The answer is b. Decreased FREMITUS.** Patient had pneumonia. Pneumonia: An acute infection of lung parenchyma including alveolar spaces and interstitial tissue. During physical examination most common symptoms include ronchi, percussion dullness, decreased breathing sounds and INCREASED fremitus..
3. **The answer is a. Wheezing . Lung abscess** characterized by INCREASED FREMITUS, dullness by percussion, decreased breath sounds and no **Wheezing** .
4. **The answer is d. dullness by percussion.** See #1.
5. **The answer is b.** it is dullness by percussion on right side. Fibrous Plevritis is characterized by absence pleural effusion, presens of pleural friction rub, inflammation with many neutrophils band forms present.
6. **The answer is a. Wheezing.** Pulmonary embolus leads to development of pulmonary infarction. **Pulmonary infarction (PI)** is hemorrhagic consolidation (often followed by necrosis) of lung parenchyma with Plevritis chest pain, . Tachypnea, Hemophtysis and no wheezing.
7. **The answer is c.** Warfarin is the principal agent recommended for the prophylaxis of acute pulmonary embolus in patient who receive total hip replacement. Warfarin is started preoperatively, the daily dose is adjusted to maintain an international normalized ratio (INR) of 2 to 3. The value of aspirin in this setting is unclear. Early ambulation and elastic stockings are also important in preventing thromboembolism, but are not adequate in themselves in this high-risk situation.
8. **The answer is b. Airway obstruction** is reversible. All others is present in all obstructive airway diseases.
9. **The answer is a. dullness by percussion.** Bronchial **asthma** characterized by emphysema and **hyperresonant** by percussion, tachypnea, clubbing of fingernails, wheezes, eosinophilia.
10. **The answer is a. bradipnoe,** The patient have pneumonia that characterized by fin crackles haemophtisis, dullness by percussion, increased breath sounds.

## Study question

1. While taking a PMH, the clinician learns that a patient is taking digoxin, a cardiac medication. The clinician should
  - (A) list the digoxin in the PMH
  - (B) find out about the cardiac symptom and put it in the PMH
  - (C) find out how long the patient has been taking the digoxin
  - (D) find out about the cardiac symptom and put it in the ROS
  - (E) find out about the cardiac symptom and put it in the HPI
  
2. The patient complains that; the pain starts when doing aerobics, lasts for 10 minutes, is like a dull, achy pressure, occurs nightly, two or three times a week for the past 3 weeks, The pain increases if the patient does not stop aerobics. That pain is:
  - A. Stenocardia
  - B. Myocardium Infarction
  - C. Chest radiculitis
  - D. Other neurologic disorder
  
3. In preparing a problem list for a new patient with a proven myocardial infarction, all of the following information should be relegated to the inactive problem list EXCEPT
  - (A) hysterectomy, 1976
  - ( B ) diabetes mellitus
  - (C) x-ray confirmed duodenal ulcer, 1984
  - (D) right hip fracture, 1988
  - ( E ) pneumococcal pneumonia, 1989
  
4. An appropriate screening test for a 40-year-old asymptomatic man who **presents for a** health evaluation is
  - (A) hemoglobin and hematocrit,
  - (B) serum cholesterol
  - (C) thyroid function tests
  - (D) serum electrolytes
  
5. The patient is a 55-year-old woman with diabetes and coronary artery disease. She continues to work at her secretarial position at an insurance company and lives with her husband in a two bedroom apartment. She is fatigued easily and takes frequent naps. She appears alert and well nourished. The above description includes all of the following factors EXCEPT
  - (A) diagnosis (B) prognosis (C) symptoms (D) ADLs ( E ) signs

### Questions 6-10

For each clinical situation described below, select the single most useful laboratory test.

- (A) EKG
  - ( B ) Chest x-ray
  - (C) CBC
  - (D) Echocardiogram (E) None of the above
- 
- 6. A 33-year-old lawyer with cough, fever, and pleuritic chest pain of 3 day's duration
  - 7. A 62-year-old male construction worker with a 2-hour history of crushing substernal chest pain
  - 8. A 23-year-old student with sudden onset (1 hour ago) of left sided chest pain and shortness of breath. Found to have absent breath sounds over the left hemithorax
  - 9. A 40-year-old woman with a 3-hour history of "palpitations" who is found to have a heart rate of 160/min
  - 10. A 72-year-old woman with a diffuse petechial rash

## Answers and explanations

**1. The answer are: *The answer E.*** Any problem or symptom for which patients are currently being treated should be included in the HPI and have the seven parameters determined. Digoxin

is a cardiac medication that cannot be forgotten and put in the PMH. Any cardiac symptom needs to be uncovered and reported in the HPI.

**2. The answer is A.** The pain that occurs when patient doing exercises, lasts seven minutes, is like a dull, achy pressure, occurs nightly, increases if the patient does not stop aerobics is stenocardia.

**3. The answer is B.** The presence of diabetes must be kept in mind at all times in the management of the patient, regardless of the nature of the presenting problem. The hysterectomy and hip fracture are legitimate inactive problems and of no concern now, but they must remain as part of the patient's comprehensive medical history. The duodenal ulcer may recur, so it must be noted. The pneumonia is not a problem now, but since pneumococcal disease *may* indicate a specific lack of resistance to this organism, it must be carried forward on the inactive problem list.

**4. The answer is B.** The only blood test recommended for both men and women at any age is a serum cholesterol obtained every 5 years. Hemoglobin and hematocrit are not warranted for men but may be important in menstruating women. Thyroid function tests are unnecessary on asymptomatic men but may be tested in asymptomatic older women. Serum electrolytes are never recommended as a routine. Fasting serum glucose is also not recommended routinely and should be ordered only if symptoms warrant it.

**5. The answer is B.** Symptoms are any problems experienced by the patient, which may be used to identify the underlying pathology. Signs are physical indications of the disease, which may be visible to anyone or specifically to the clinician. Diagnosis is the underlying cause of any signs or symptoms. ADLs are a measure of a patient's level of functioning. Prognosis is the predicted course of a disease or condition.

**6-10. The answers are: 6-B, 7-A, 8-B, 9-A, 10-E.**

**6. "B"** The combination of symptoms, such as cough, fever, and pleuritic chest pain, in a young person are highly suggestive of pneumonia, a diagnosis best confirmed by chest x-ray.

**7. "A"** Crushing substernal chest pain is the classic symptom of myocardial infarction. The EKG may be definitive and, if not, is certainly essential to monitoring the course of the illness or beginning the process of "ruling out" the most dangerous diagnostic possibility.

**8. "B"** The combination of historical data and physical findings (i.e., sudden onset of shortness of breath) are most consistent with spontaneous pneumothorax. It is essential for the proper care of the patient to establish that pneumothorax is present and to determine the degree of the lung compromise.

**9. "A"** A heart rate of 160/min demands a definition of the conduction problem present. The proper choice of therapeutic intervention requires a knowledge of the source of the tachycardia (atria) or ventricular, which can usually be defined from a rhythm strip or a 12-lead EKG.

**10. "E"** Petechial rashes are secondary to platelet problems until proven otherwise. This woman's problem may be either inadequate platelet numbers or dysfunction of platelets. The most important test in this situation is a platelet count.

## Stady question

The clinician is sent to the hospital ward to do a workup on a newly admitted 32-year-old patient with the CC of abdominal pain and a working diagnosis of acute pancreatitis.

1. The primary data base should include all of the following information EXCEPT

- (A) complete medical history
- ( B ) physical examination
- C) working problem list
- (D) tentative plan
- ( E ) final diagnosis

2. The most important part of the physical examination on this patient is the abdominal assessment. All of the following maneuvers are likely to yield useful information EXCEPT

- (A) palpation of the liver

- ( B ) palpation of the gallbladder
- (C) palpation for upper abdominal tenderness
- (D) palpation of the abdominal aorta
- ( E ) assessment of the bowel sounds

3. The clinician finds diffuse abdominal tenderness and guarding on examination as well as a liver span of 18 cm. The problem list should include all of the following conditions EXCEPT

- (A) possible alcohol abuse
- ( B ) abdominal pain
- (C) acute pancreatitis
- (D) abdominal tenderness and guarding
- ( E ) hepatic enlargement

4. 8. The clinician is asked to present this case to the ward attending. The presentation must include all of the following information EXCEPT the

- (A) HPI
- ( B ) alcohol consumption history
- (C) patient's vital signs
- (D) FH of alcohol consumption
- ( E ) abdominal examination findings

#### Questions 5-8

For each of the case scenarios presented below, choose the most likely body system implicated.

- (A) Musculoskeletal
- (B) Renal-urinary
- (C) Respiratory
- (D) Reproductive
- (E) Gastrointestinal

5. A 23-year-old runner comes to the outpatient department with a complaint of persistent pain in the left knee and calf since Sunday's marathon.

6. A 72-year-old hypertensive man comes into the emergency room with acute shortness of breath, cyanosis, and rales throughout both lung fields.

7. A 32-year-old woman who has been taking high doses of calcium to prevent osteoporosis comes in with a 2-hour history of excruciating left flank pain.

8. A 25-year-old man comes to the clinic with a 3-day history of 10-12 loose stools a day, which began while he was camping in the Rocky Mountains.

9. In what order should the abdominal examination sequence proceed?

- i A) Inspection, auscultation, palpation, percussion (B) Inspection, palpation, auscultation, percussion (C) Inspection, palpation, percussion, auscultation (D) Inspection, percussion, auscultation, palpation ( E) Palpation, auscultation, inspection, percussion.

10. The effectiveness of the spleen examination is improved by all of the following factors EXCEPT

- (A) a thin patient
- (B) asking the patient to take slow deep breaths
- (C) advancing the examiners fingers on expiration
- (D) asking the patient to roll on the left lateral decubitus
- (E) asking the patient to place his or her left hand under the left buttocks.

## Answers and explanations

**1. The answer is E.** [Chapter 10 II; IV A 1] The data base always includes a complete medical history, physical examination, problem list, and usually a preliminary plan. The primary data base should never include a definitive diagnosis because the supporting data have not been obtained. It is potentially hazardous to jump to a final diagnosis as a part of primary data collection.

**2. The answer is D.** [Chapter 6 III OJ] The probability of a 32-year-old having abdominal aortic disease as the basis for his abdominal complaints is remote. On the other hand, general assessment for signs of acute inflammation or viscus perforation are rational and essential. For further information on assessment for the complaint of abdominal pain, see any standard surgical textbook.

**3. The answer is C.** [Chapter 10 II A] At this stage of the data collection, symptoms and signs are known at a level that does not allow a diagnosis. The problems should be listed at the level at which they are absolutely definable.

**4. The answer is D.** [Chapter 11 VII C, D] The oral case presentation should include all of, but no more than, the data necessary for resolution of the

patient's immediate problems. The FH of alcohol consumption is a second level of information, which is not critical to the immediate management of the acutely ill person being discussed.

**5-8. The answers are: 5-A, 6-E, 7-B, 8-E.** Young adult~, are commonly seen for traumatic injuries to the muscles and joints, especially those individuals who are strenuously physically active. The temporal relationship to the marathon should alert the clinician to the high probability of a musculoskeletal problem.

Despite the fact that this 72-year-old man presents with what appear to be respiratory problems, the history of hypertension, the acuteness of the problem, and the deoxygenation all suggest cardiac failure manifested as acute pulmonary edema in which the failing system is the cardiovascular with the respiratory system being only secondarily involved.

Flank pain may be generated from the gastrointestinal tract, the pelvic organs (reproductive), or the urinary system. The history of high calcium intake and the magnitude of the pain is most suggestive of ureteral stone, a common complication of excessive calcium intake in otherwise healthy individuals.

Acute diarrhea must be related to the gastrointestinal system, either as a primary infectious or inflammatory disorder or secondary to endocrine or systemic disease. The acuteness of the problem and its temporal relationship to a mountain camping trip are suggestive of an ingested organism, which has caused local bowel symptoms.

Amenorrhea in a healthy sexually active woman is pregnancy until proven otherwise. The primary system to be considered here is the reproductive, and the first tests are those for pregnancy. If pregnancy is disproven, then further consideration of less common causes for amenorrhea may be pursued.

**9. The answer is A.** careful detailed inspection should be the first component of every examination. The examination sequence for the abdominal examination differs from that of the chest or cardiac examination. Auscultation must come before palpation and percussion. Palpation and percussion may alter bowel sounds (i.e., decrease or increase their intensity). Auscultating first gives a more accurate representation of true bowel sounds.

**10. The answer is D.** Even normal spleens may be palpable in a thin patient. The technique of the examination is to have the patient take slow deep breaths and advancing fingers on expiration. The spleen becomes easier to palpate if the patient rolls to the right lateral decubitus position or places his or her left hand under the left buttock.

## Study questions

### **5. Normal adults excrete proteins:**

- E. Less than 150 mg/24-hour period
- F. Less than 1 mg/24-hour period
- G. More than 150 mg/ 24-hour period
- H. More than 500 mg/ 24-hour period

### **6. Normal urine usually contains only one from following components detectable with commercially available dipsticks :**

- F. Blood
- G. Glucose
- H. Ketonic bodies
- I. Proteins
- J. Bilirubin

### **7. Urinary sediment from normal urine preparing by centrifugation contains only one from following components:**

- E. Bacteria**
- F. Erythrocytes**
- G. More than 1-3 leukocytes**
- H. Casts**

**8. Urine output less than 100 ml/day is:**

- E. Oliguria**
- F. Polyuria**
- G. Nocturia**
- H. Anuria**

### **Questions 5-8**

**For each of the case scenarios presented below, choose the most likely body system implicated.**

- (A) Musculoskeletal**
- (B) Renal-urinary**
- (C) Respiratory**
- (D) Reproductive**
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8. A 25-year-old man comes to the clinic with a 3-day history of 10-12 loose stools a day, which began while he was camping in the Rocky Mountains.

### **And of group question**

**9. Acute renal failure is accompanied with all phenomena besides one:**

- A. Anuria**
- B. Serum urea more than 8 mMol/l**
- C. Glomerular filtration rate less than 50 ml/min.**
- D. Serum creatinine more than 120 mcMol/l**

**10. Diseases of the kidney are accompanied with all phenomena besides one:**

- A. Hypertension**
- B. Proteinuria**
- C. Cough**
- D. Erythrocyturia**
- E. Leukocyturia**

## Answers and explanations

1. **The answer is “A”** Protein usually is not present in normal urine above 150 mg/day. Proteinuria about 500 mg/day indicates kidney damage.

2. **The answer is “C”** Ketonic bodies are present in the urine of healthy individuals during fasting. Blood, Proteins, Bilirubin detectable with commercial dipsticks are not present in urine of healthy persons.

3. **The answer is “A”** Bacteria are present in small quantities in normal urine sediments. Erythrocytes, Leukocytes (more than 1-3), Casts - are not.

4. **The answer is “D”** Urine output less than 100 ml/day is Anuria. Oliguria –urine output less than 500 ml/day. Polyuria is more than 2l urine a day. Nocturia – more urine at night than per day.

5-8. **The answers are: 5-A, 6-E, 7-B, 8-E.** Young adult~, are commonly seen for traumatic injuries to the muscles and joints, especially those individuals who are strenuously physically active. The temporal relationship to the marathon should alert the clinician to the high

probability of a musculoskeletal problem.

Despite the fact that this 72-year-old man presents with what appear to be respiratory problems, the history of hypertension, the acuteness of the problem, and the deoxygenation all suggest cardiac failure manifested as acute pulmonary edema in which the failing system is the cardiovascular with the respiratory system being only secondarily involved.

Flank pain may be generated from the gastrointestinal tract, the pelvic organs (reproductive), or the urinary system. The history of high calcium intake and the magnitude of the pain is most suggestive of ureteral stone, a common complication of excessive calcium intake in otherwise healthy individuals.

Acute diarrhea must be related to the gastrointestinal system, either as a primary infectious or inflammatory disorder or secondary to endocrine or systemic disease. The acuteness of the problem and its temporal relationship to a mountain camping trip are suggestive of an ingested organism, which has caused local bowel symptoms.

Amenorrhea in a healthy sexually active woman is pregnancy until proven otherwise. The primary system to be considered here is the reproductive, and the first tests are those for pregnancy. If pregnancy is disproved, then further consideration of less common causes for amenorrhea may be pursued.

**9. The answer is “C”** Glomerular filtration rate more than 115 ml/min. Anuria is main sign of the acute renal failure. Serum urea more than 8 mMol/l, Serum creatinine more than 120 mcMol/ are signs of the asotemia by the acute renal failure.

**10. The answer is “C”** Cough is sign of lung diseases. Hypertension, Proteinuria, Erythrocyturia, Leukocyturia – all are symptom's of the kidney diseases.

#### STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. Iron deficiency can develop in all of the following clinical conditions EXCEPT

- (A) nontropical sprue
- (B) excessive menstrual flow
- (C) bacterial endocarditis
- (D) occult colonic carcinoma
- (E) pulmonary hemosiderosis

3. Normal or increased bone marrow iron stores are found in all of the following forms of hypochromic, microcytic anemia EXCEPT

- (A) anemia caused by lead intoxication
- (B) sideroblastic anemia
- (C) iron deficiency anemia
- (D) anemia associated with rheumatoid arthritis

2. A 58-year-old woman who complains of easy fatigue and weakness is found to be mildly anemic, presenting with a hemoglobin level of 10 g/dl and ferritin of 16 ng/dl. Of the following courses of management, which one is best suited to this patient?

- (A) Encourage the maintenance of a well-balanced diet and monitor the anemia
- (B) Prescribe oral ferrous sulfate for 6 months to replace iron stores
- (C) Prescribe sustained-release iron capsules to avoid gastrointestinal discomfort and help ensure patient compliance
- (D) Order bone marrow studies to identify iron deficiency as the source of the anemia
- (E) Order stool analysis to detect the presence of occult blood

**Directions:** Each item below contains four suggested answers, of which **one or more** is correct. Choose the answer

**A** if 1, 2, and 3 are correct

**B** if 1 and 3 are correct **C** if 2 and 4 are correct **D** if 4 is correct

**E** if 1, 2, 3, and 4 are correct

4. Failure of a microcytic anemia to respond to oral iron replacement may be due to

(1) presence of an inflammatory bowel condition (2) malabsorption of iron (3) continued blood loss (4) sustained-release iron preparation

5. Causes of anemia of chronic disease (ACD) include which of the following?

- (1) Uncomplicated diabetes mellitus (2) Tuberculosis
- (3) Hypertension
- (4) Rheumatoid arthritis

1-C 4-E 2-E 5-C 3-C

## ANSWERS AND EXPLANATIONS

**1. The answer is C** [IV A 1; Table 5-21].

Iron deficiency does not develop in bacterial endocarditis. Iron stores can be depleted by nontropical sprue, excessive menstrual flow, occult colonic carcinoma, and pulmonary hemosiderosis. Bacterial endocarditis and other chronic diseases that cause anemia are characterized by the increased storage of iron in the bone marrow but poor iron reutilization. Iron stores can be depleted by three mechanisms: inadequate iron intake (as in infants who are fed an unsupplemented diet of milk), iron malabsorption (as in patients with tropical or nontropical sprue), and chronic occult blood loss (as in cases of excessive menstrual bleeding, occult gastrointestinal bleeding in colonic carcinoma, or increased blood loss through the respiratory tract in pulmonary hemosiderosis).

**2. The answer is E** [IV E 1 a].

The best course of action to take in the management of this woman is to order stool analysis to detect the presence of occult blood. Although it is important to replace iron stores in an iron-deficient patient, it is more important to identify and treat the underlying cause of the deficiency. This is especially true for older patients in whom iron deficiency may be the presenting sign of a more serious disorder, most commonly occult gastrointestinal bleeding and malignancy. Therefore, stool analysis to detect the presence of occult blood is the best course of action in the management of this 58-year-old woman. Iron replacement should also be instituted, preferably with oral ferrous sulfate, since it contains 60 mg of elemental iron in each 300 mg tablet, is well absorbed, and is inexpensive. Administration of sustained-release forms of oral iron should not be the first choice for the management since they are not well absorbed. Bone marrow studies may be required at some point in the patient management, but they should not be used as the first step in determining the cause of the iron deficiency. Diet alone cannot supply enough iron to replace deficient stores.

**3. The answer is C** [IV A, IX A 3, X B 3].

Normal or increased bone marrow stores are not found in iron deficiency anemia. The basic defect in hypochromic, microcytic anemia is a quantitative reduction in the synthesis of hemoglobin, which ultimately results in the production of red cells with reduced hemoglobin contents. Disorders of hemoglobin synthesis may involve either the heme component or the globin component. In iron deficiency, there are insufficient marrow iron stores for optimal heme synthesis, which results in hypochromic anemia. In lead poisoning, heme synthesis is impaired by the presence of lead, which inhibits the activity of certain critical enzymes; however, iron stores in the bone marrow are abundant. Sideroblastic anemia refers to a diverse group of disorders that all have impaired heme synthesis; the ultimate result is hypochromic anemia and iron loading. Anemia of chronic diseases such as rheumatoid arthritis is associated with increased iron storage with impaired iron reutilization for heme synthesis.

**4. The answer is E (all)** [IV A 3, E 5].

A patient may not respond to iron therapy for several reasons. The presence of an underlying chronic disease is the most common cause of a patient's failure to respond to iron therapy. Patients who do not absorb iron well *may* also have a malabsorption syndrome or subtotal gastrectomy, in which an insufficient amount of gastric acid interferes with the conversion of iron from the dietary to soluble form. Oral iron therapy may not be sufficient to replace the iron lost through the continued bleeding that occurs in such conditions as hereditary telangiectasia. Sustained-release iron preparations may be prescribed to avoid the gastrointestinal discomfort often associated with oral iron therapy. However, not enough iron may be available in the duodenum, where absorption should occur.

**5. The answer is C (2 and 4)** [VI B 1 a, b].

Anemia of chronic disease (ACD) can be caused by both tuberculosis and rheumatoid arthritis, which are inflammatory diseases in which there are activated macrophages in the reticuloendothelial system. This activation stimulates the secretion of apolactoferrin, an iron-binding protein found in phagocytic cells, into the circulation. Apolactoferrin promotes both the removal of circulating ferritin and the formation of hemosiderin, the storage form of iron. Iron stored as hemosiderin is less accessible for the synthesis of hemoglobin in erythroid cell precursors. Patients with diabetes mellitus may be highly susceptible to infections, but there is no underlying activation of the phagocytic cells. Hypertension is also not considered an inflammatory disease, and no relationship to ACD has been noted.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. All of the following statements are true of patients with pernicious anemia (PA) EXCEPT

2. All of the following findings are present in both folate and vitamin B<sub>12</sub> deficiencies EXCEPT

- (A) macrocytic red cells
  - (B) peripheral neuropathy
  - (C) Howell-Jolly bodies and Cabot's rings in the bone marrow
  - (D) high levels of lactate dehydrogenase (LDH) and indirect bilirubin resulting from ineffective erythropoiesis
  - (E) hypersegmented neutrophils with six or seven lobes
- (A)

(B) (C) (D) (E)

about 75% of PA patients exhibit anti-intrinsic factor antibodies in serum

PA is associated with another autoimmune disease called Hashimoto's thyroiditis

older vegetarians develop PA because of disuse of intrinsic factor

about 90% of patients display antibodies to gastric parietal cells

PA is a consequence of long-standing gastritis, which leads to atrophy of the secretory cells of the stomach

**Directions:** Each group of items in this section consists of lettered options followed by a set of numbered items. For each item, select the **one** lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

### Questions 3-6

For each patient with megaloblastic anemia, select the associated cause or finding.

- (A) Alcoholism
- (B) Subacute combined degeneration of the spinal cord
- (C) Abnormal results for the three parts of the Schilling test
- (D) Bilobate polymorphonuclear cells
- (E) Blind loop syndrome

3. A 54-year-old white male with chronic peptic ulcers and a previous gastrectomy presents with anemia, a mean corpuscular volume (MCV) of 110 fl, a red beefy tongue, a normal level of serum folate, a low level of serum vitamin B<sub>12</sub>, and a normal neurologic examination.

4. A 43-year-old man presents with anemia, a MCV of 101 fl, a platelet count of 70,000/μl, a low level of serum folate, and a normal serum level of vitamin B<sub>12</sub>.

5. A 72-year-old woman who presented to a neurologist with complaints of falling is found to have anemia, a MCV of 115 fl, a platelet count of 50,000/μl, a white blood cell count (WBC) of 2200/μl, an elevated level of serum folate, and a low serum level of vitamin B<sub>12</sub> (20 ng/L).

6. A 45-year-old woman who had multiple bowel surgeries for Crohn's disease presents with anemia, a MCV of 110 fl, a WBC of 5700/μl, a platelet count of 150,000/μl, and a normal serum level of vitamin B<sub>12</sub>.

**1. The answer is C [III D 3 b].**

Vegetarians do well with the oral replacement of vitamin B<sub>12</sub> and develop megaloblastic anemia as a consequence of a lack of animal-derived food in their diet and not because of abnormal intrinsic factor. Rather pernicious anemia (PA) is a consequence of chronic gastritis, which causes atrophy of the stomach secretory

cells. Most PA patients display anti-intrinsic factor antibodies in serum, saliva, and gastric juice as well as antibodies to the cytoplasm of gastric parietal cells. This evidence, as well as an association with other immune disorders in these patients such as Hashimoto's thyroiditis (antibodies to thyroid tissues), points to the possibility of an autoimmune mechanism for PA.

**2. The answer is B** (*III B, D 1, 2*).

Both folate-deficient and vitamin B<sub>12</sub>-deficient patients exhibit macrocytic red cells, Howell-Jolly bodies and Cabot's rings in the marrow, high levels of lactate dehydrogenase (LDH) and indirect bilirubin resulting from ineffective erythropoiesis, and hypersegmented neutrophils displaying six or seven lobes. However, only vitamin B<sub>12</sub>-deficient patients develop neurologic abnormalities because vitamin B<sub>12</sub> is required in myelin metabolism.

**3-6. The answers are 3-E** (*III C 1, 3, D 2 b, 3 d; Table 6-2*), **4-A** (*III D 1 b(1), (4) (a)*), **5-B** (*II B 2, C, • III D 3 c*), **6-C** (*III D 2 b (3), 3 d(4)*).

A patient with megaloblastic anemia and a previous history of gastrectomy should respond positively to part II of the Schilling test. However, the development of blind loop syndrome is common in gastrectomy patients and will cause a negative response to part II. This condition should respond favorably to antibiotic administration and result in a normal part III response.

Folate deficiency in patients from Western countries who present with megaloblastic anemia is most likely due to alcoholism. Alcohol also directly suppresses bone marrow activity and may decrease the platelet counts.

In severe vitamin B<sub>12</sub> deficiency in pernicious anemia (PA), subacute combined degeneration of the spinal cord and pancytopenia manifest as neurologic symptoms. Poor conjugation of folate allows it to escape from cells into the bloodstream, causing elevated levels of serum folate (the folate trap hypothesis).

Surgical resection of the distal part of the ileum in patients with Crohn's disease is very common. The distal ileum is the site of absorption of vitamin B<sub>12</sub>. The absorption deficit will not be corrected by the administration of antibiotics in part III of the Schilling test.

**7-10. The answers are 7-D** (*III D 3 d*), **8-A** [*I A 4, B 2 a (2); III D 2 b (1), 3 d (4) (a)*], **9-B** (*III D 1 b (3) (a), 3 d (4)*), **10-E** (*III D 2 b (4), 3 d (4)*).

The typical findings in a patient with pernicious anemia (PA) are a low serum level of vitamin B<sub>12</sub>, a normal or elevated level of serum folate, and a failure to absorb orally administered radiolabeled vitamin B<sub>12</sub> (an abnormal response to part I of the Schilling test) that is corrected with the addition of intrinsic factor (a normal part II response).

Patients who adhere to a strict vegetarian (vegan) diet may display a low serum level of vitamin B<sub>12</sub>, which is available only in food of animal origin, and a high level of serum folate (vegetables are a rich source of folate, and its concentration is increased by the vitamin B<sub>12</sub> deficiency). The result for part I of the Schilling test is normal since there is no abnormality associated with the absorption of oral

vitamin B<sub>12</sub>

Pregnancy can cause folate deficiency by increased utilization of the easily depleted stores. Stores of vitamin B<sub>12</sub> are much larger and not so easily depleted. The Schilling test would not be indicated in this patient and would show normal results if performed.

Infestation with the fish tapeworm (*Diphyllobothrium latum*) can cause vitamin B<sub>12</sub> deficiency as the parasite utilizes vitamin B<sub>12</sub> passing through the intestine. This condition cannot be corrected by the administration of oral antibiotics unless they are prescribed specifically to treat this infestation. Therefore, the result for part III of the Schilling test would be abnormal.

1-C 4-A 2-B 5-B 3-E 6-C

## Study question

Which from the stated below symptoms, concepts, terms mostly belong physiology and pathology:

- A. Pancreatic islets
- B. Thyroid gland
- C. Parathyroid glands
- D. Adrenal glands
- E. Hypophysis

- |                            |   |
|----------------------------|---|
| 27. Acromegalia            | 40. Nephroangiopathia                         |
| 28. Exophthalmia           | 41. Thyrotropine                              |
| 29. Cramps                 | 42. Gangrene of foot                          |
| 30. Insulin                | 43. Mixedema                                  |
| 31. Parathormon            | 44. Chloride of calcium intravenous at cramps |
| 32. Glucagon               | 45. Cortisol                                  |
| 33. Prolactin              | 46. Hyperglycemia                             |
| 34. 3.3 – 5.5 Mmol/l       | 47. Cysto-fibrous osteopathy                  |
| 35. Ketoacidosis           | 48. Adrenalin                                 |
| 36. Icenko-Cushing Disease | 49. Proteinurea                               |
| 37. Aldosteron             | 50. Iodine                                    |
| 38. Glucosurea             | 51. Polyuria                                  |
| 39. Thyroxin               |   |

### Answers and explanations

1.E, 2. B, 3. C, 4. A, 5. C, 6. A, 7. E, 8. A, 9. A, 10. E, 11. D, 12. A, 13. B, 14. A, 15. E, 16. A, 17. B, 18. C, 19. D, 20. A, 21. C, 22. D, 23. A, 24. B, 25. E.

2. Acromegalia (1) - hyperproduction of the somatotropine, Prolactin (7), Icenko-Cushing Disease – hyperproduction of the corticotropine (15). All of them are hormones of anterior lobe of hypophysis. Polyuria to 30 l/ day is symptom of deficit antidiuretic hormone (vasopressine) that concentrate at posterior lobe of hypophysis (25).
2. Thyroxin (13) – hormone of the thyroid gland, Iodine (24) is in it molecule. Exophthalmia(2) , Mixedema(17) – symptoms of disorders of this gland.
6. Cramps(3) – symptom of deficit of calcium by hypoproduction of Parathormon(5), Chloride of calcium intravenous at cramps (18) -
7. Insulin (4) and Glucagon (6) hormones of islets of pancreas 3.3 – 5.5 Mmol /l (8), Hyperglycemia (2 (20) symptom of diabetes mellitus – deficit of insulin. , Ketoacidosis (9), Nephroangiopathia 14), Gangrene of foot (16) – all are complications of diabetes mellitus,
8. Aldosterone (11), cortisol(19), Adrenaline (22) – all are hormones of adrenal gland.

Tests to **practicum**: “Allergic and immune system disorder patients examination“

### Which from the stated below assertions, concepts, and clinical situations are associated only with the allergic reactions:

- A. I type
  - B. II and the III type
  - C. IV type
  - D. all types
  - E. are not the allergic reactions
9. In 15 minutes after introduction of novocaine for anaesthetizing of extraction of tooth patients blood pressure fell down to 60/0 mm Hg.
  10. In three days after setting of chloramphenicol to the patient with festering paradontite in the blood test absent eosinophils, basophils, band neutrophils and sharply diminished segmented neutrophils. Necrotic quinsy began.
  11. The Mantu Reaction
  12. Poststreptococcal glomerulonephrites
  13. Hay fever
  14. Urticaria
  15. The Gregersen Reaction
  16. Bronchial asthma
  9. sharp rhinitis in 5 minutes after the contact with pollen of plants
  10. Heavy defeat of mucus shell of mouth cavity after chewing of pill of antibiotic

Which from the stated below disorders gave to do to some system:

- A. Skin, subderma and mucus shells
- B. Cardio-vascular system
- C. Alimentary tract and kidney
- D. Respiratory tract
- E. Hematology

11. Hay fever
12. Anaphylaxis
13. Glomerulonephritis
14. Bronchial asthma
15. Sharp diffuse myocarditis
16. Sharp rhinitis
17. Gingivitis
18. Autoimmune hemolytic anemia
19. Medicament's agranulocytosis
20. Angioedema
21. Allergic vasculites
22. Stomatites
23. Ulcerous colitis

#### Answers and explanations

24. Answer (A) collapses by anaphylaxis.
25. Answer (B) –reaction antigen-antibody on surface of blood cells
26. Answer (C) –reaction of sensibilisate lymphocytes
27. Answer (B)– immunocomplex disease
28. Answer (A) – pollinosis – IgE reaction
29. Answer (D)– pollinosis – IgE reaction
30. Answer (E) – Gregersen reaction light bloody stool
31. Answer (D)- all type reaction
32. Answer (A) - pollinosis – IgE reaction
33. Answer (D) - pollinosis – IgE reaction
34. Answer (A) - mucus
35. Answer (B) - collapse
36. Answer (C) -kidney
37. Answer (D) –respiratory tract
38. Answer (B) -myocarditis
39. Answer (A) - mucus
40. Answer (A) - mucus
41. Answer (E) - blood
42. Answer (E) -blood
43. Answer (A) - subcutaneous
44. Answer (B) –vascular
45. Answer (A) - mucus
46. Answer (C) – alimentary tract

## Approach to Clinical Problem Solving

**INTRODUCTION.** Once the student has mastered the basic data-acquisition skills-interviewing, taking the medical history, and conducting the physical examination-the next challenge becomes that of **putting the data to work**. From the medical history and physical examination, the student must develop a **problem list**; from the problem list, the student must develop a **differential diagnosis**; and from the differential diagnosis, **diagnostic** and **management plans** evolve. This chapter presents a sequential method of organization and planning for action based upon the information available.

**II. PROBLEM LIST.** Unlike the differential diagnosis, the problem list is not speculative. It is a tabular list of the patient's problems defined at any given time. The problem list is **primary, reduced to concrete terms, and dynamic**. Ongoing modification of the problem list as data are obtained and as the patient's condition changes is an efficient and accurate way of communicating to the health care team the immediate status of the patient.

**A. Definition of a problem.** A problem is anything that demands action (**active problem**) or requires notation because it is essential to the comprehensive care of the patient (**inactive problem**). Active problems can require action at one or more of three levels:

**1. Diagnostic action.** This category includes unresolved problems, including symptoms, signs, or abnormal laboratory tests, that cannot be converted into plans for management or resolution without additional data. Only when a definite cause for the problem is defined may it be converted to a diagnosis or rendered inconsequential (inactive or resolved).

**a. A symptom**, such as shortness of breath, the cause of which is unclear, may constitute a

problem. If the cause is not absolutely known, the symptom must be listed **at the level at which it is absolute**-that is, as "shortness of breath."

**b. A sign**, such as sinus tachycardia, is listed as a problem if its cause is unknown or if either

the patient or the clinician feels it needs further diagnostic workup.

**c. A laboratory finding**, such as hypokalemia or hypernatremia, may be defined as a problem.

**2. Therapeutic action.** If a symptom, sign, or abnormal laboratory test is either sufficiently well understood to justify treatment or is clearly threatening to the patient's well-being, it may be entered as a problem requiring therapeutic action.

**a. Known diagnosis with dangerous presentation.** A patient with known diabetes mellitus may present with hyperglycemia and acidosis. Since the cause of the abnormal laboratory values is presumed to be the underlying disease and since both abnormalities require immediate therapy, the problem may be entered as "diabetes mellitus with hyperglycemia and metabolic acidosis."

**b. Unknown diagnosis with dangerous presentation.** Occasionally, a problem requires therapeutic action for the patient's safety, even when its basis is not clearly understood. For example, a child with a history of febrile convulsions may present with a temperature of 105° F, necessitating antipyretics while the cause of the fever remains unknown. Thus, the single problem, "fever," demands both treatment *and* further diagnostic workup simultaneously.

### **3. Patient education**

**a. Preexisting problems** may need to be reviewed with the patient.

**b. Diagnostic or therapeutic intervention** may need a patient's contractual agreement. **c. A discussion of prognosis** with long-term management plans is necessary.

## **B. Derivation of the problem list**

**1. Medical history.** After acquiring, recording, and reviewing the medical history, the clinician may begin to identify problems, most of which will fall into one of three groups: **a. Preexisting diagnoses**

**b. New or unresolved symptoms or signs**

**c. Social, health habit, or financial problems.** Known or suspected drug allergies, tobacco or alcohol abuse, and unemployment, leading to financial or social problems, may all be defined as problems that require some level of intervention or education.

**2. Physical examination.** Upon review of the physical examination, **all abnormalities** requiring some sort of action and inactive problems requiring notation, such as a surgical scar that indicates the patient no longer has an appendix, should be listed at the level at which their implications are understood.

**3. Laboratory data base.** If laboratory data have been obtained, they are scanned for abnormalities. The primary problem list is updated if these are entered as independent problems requiring action.

## **C. Discriminating active from inactive problems**

**1. Active problems.** The active problem list should be separated from the inactive list, so that any reader can clearly discriminate between the two. Double columns with active problems on the left and inactive problems on the right facilitate the conversion of an active problem to an inactive one simply by using an arrow from one column to another (see Figure 10-1).

**2. Inactive problems.** There is no consensus among clinicians about the need to maintain an inactive problem list. However, since this chapter is concerned with the comprehensive data base, which should be available on every patient, an inactive problem list is described. The list should include all concurrent conditions, which might conceivably resurface or alter consideration of an active problem, and all past conditions, ignorance of which might affect the approach to the active problems. Examples of valid inactive problems in a patient with a broken hip include:

**a. Positive PPD.** The knowledge of the PPD positivity is essential to full awareness of potential problems in this patient.

**b. Organ removal** [usually designated as "S/P (status-post) cholecystectomy"]. Although this might not be important to the patient's broken hip, it may be important if the patient presents later with an acute abdomen.

**D. Modifying and updating the problem list.** The problem list is intended to be a comprehensive, dynamic, and up-to-date summary of the patient's status. As the patient's problems are refined and altered, so must items on the problem list be either subsumed, resolved, or inactivated.

**1. Subsumption of a problem.** As the diagnostic workup proceeds or as therapeutic interventions change the course of the illness, separate problems on the primary list may be clarified as belonging to a single diagnosis.

a. When the health care team becomes certain that problems can be grouped, a cluster of symptoms, signs, or abnormal laboratory results may be **subsumed** under a single heading. For example, a patient presenting to the emergency room may have the following primary problem list:

- (1) **Problem 1:** Shortness of breath
- (2) **Problem 2:** High blood pressure
- (3) **Problem 3:** Peripheral cyanosis
- (4) **Problem 4:** Bilateral pulmonary rales
- (5) **Problem 5:** Low serum oxygen saturation

b. Although members of the health care team may suspect acute pulmonary edema as the basis for all of these symptoms and signs, they may not be comfortable ascribing all of them to a single problem until a chest x-ray shows the signs of pulmonary edema and a treatment trial for pulmonary edema results in resolution of all five problems. At this point, the problem list may be altered to reflect this **refinement in definition**: Problems 1-5 are now subsumed under Problem 1, which is refined from "shortness of breath" to "pulmonary edema."

## **2. Resolution of a problem**

a. When a problem **disappears completely**, either via nature or interventions of the health care team, the problem may be designated as **resolved**, usually with the date upon which the problem disappeared with no expectation of recurrence. For example, *Mycoplasma pneumoniae* in an otherwise healthy adult is placed in the resolved category when it clears completely.

- b. Caution must be exercised in designating a problem resolved if it was a symptom or sign of an underlying process, which could cause the problem to reappear; for example, acute symptoms of pulmonary edema reduced by intensive treatment are not listed as resolved until the cause of the symptom complex has also been corrected. (1) If the underlying pathology is a toxic exposure from which the patient can be protected, resolution may have been achieved. (2) If the basic pathophysiology is cardiomyopathy, the patient should be considered at risk for recurrence. Here, clinical judgment must dictate how the problem list will be modified to indicate that although the acute pulmonary edema is currently resolved, the patient remains at risk for exacerbation of the symptom complex.

**3. Inactivation of a problem.** A problem may be moved to the **inactive list** when it no longer requires intervention.

- a. A broken arm, once set and fully healed, requires no future consideration and is considered resolved.
- b. The control of pulmonary tuberculosis renders it **inactive** but not resolved; relapse is always possible.
- c. When a surgical procedure is successful, and the patient is well, resolution of the problem requiring the surgery has been achieved, but the absence or alteration of the organ involved is redesignated as inactive; for example, a gastric resection for bleeding ulcer resolves the bleeding problem, but there must be an inactive listing of the surgical procedure, such as "S/P partial gastrectomy." Absence of part of the stomach is important information for the management of any future complications related to the altered anatomy (Figure 10-1).

### **Sample Case: Derivation of the Problem List**

#### **Medical history**

L.P. is a 50-year-old female magazine editor who comes in with a 3-month history of fatigue. CC: "I am so tired all the time."

**HPI:** Patient states that she was in her usual state of health until about 3 months ago, when she began to notice easy fatigability, intermittent low-grade fever, and rare back and lower right flank pain, sometimes radiating into the right lower quadrant. These symptoms have remained static except for the fatigue, which she feels has been getting progressively worse.

#### **Problem 1: Fatigue**

Onset was insidious about 3 months ago. The symptom is characterized as "low energy." She feels inadequately rested after a night's sleep and finds that she has increasing difficulty getting through her usual 9-hour workday, the routine of meals and housework, and her night school class. She has stopped some of her social and community service activities because of the fatigue. She denies feeling sad, anxious, or depressed. Her appetite has remained good, and she has lost no weight. She finds that a

nap at midday on weekends, a new thing for her, permits her to carry out the essential functions of the day.

### **Problem 2: Low-grade fever**

When she began feeling tired, she also became aware of feeling hot and then chilly, usually at night, but sometimes in the late afternoon. She began recording her temperature 2 months ago and found that she has a 99.6-100° F temperature in the evenings several times a week. This seems to occur in cycles: 2-3 days with fever, then 2-3 days without fever. She denies shaking chills, night sweats, rashes, or sore throat. She has not been out of the United States in over 18 months. There is no known exposure to ticks or to persons with infectious diseases. She denies cough, GI symptoms, or GU symptoms over this period of time.

### **Problem 3: Back and flank pain**

The patient has had two episodes of severe right flank and right lower quadrant pain in the past 3 months. Each lasted less than 6 hours and resolved spontaneously. She sought no medical attention on either occasion and tends to minimize these symptoms. For the past month, she has been aware of vague low-back pain, which is not incapacitating. For the past week, the low-back pain has been persistent, low-grade, and has seemed to localize in the right flank with occasional pain in the right lower quadrant. She denies dysuria, gross hematuria, vaginal discharge, or painful intercourse. A urinalysis done in a walk-in clinic 1 week ago allegedly revealed red cells without pyuria or bacteriuria. No treatment was instituted. The patient finds that acetaminophen (Tylenol) minimizes the discomfort, which enabled her to continue to go to work.

The above problems are temporally related. Other than acetaminophen, she has attempted no treatment; other than the single visit to a clinic because of back pain, she has sought no medical attention and had no tests done. She came in today because the symptoms are interfering with her life and beginning to concern her that there might be something seriously wrong.

### **Problem 4: Hypothyroidism, treated**

Three years ago, because of symptoms of cold intolerance and constipation, she was seen by a clinician who made the diagnosis of hypothyroidism. Since then the patient has taken 0.1 mgm of L-thyroxine (Synthroid) daily; last thyroid function studies were done 4 months ago and, according to the patient, were normal.

### **Past medical history (PMH)**

**Hospitalizations:** Childbirth, normal vaginal delivery, 16 years ago; appendectomy, 30 years ago

**Childhood illnesses:** Measles, chicken pox, rubella, mumps; no history of rheumatic fever  
**Immunizations:** Routine and up-to-date; last DT, 4 years ago after minor skin trauma

**Allergies:** Mild fall seasonal rhinorrhea; no known drug allergies; has taken sulfa and penicillin without incident  
**Medications:** L-Thyroxine, 0.1 mgm/day (see Problem 4); over-the-counter antihistamines in the fall; acetaminophen, 1-2 tablets a day for the past 3 months

### **Family history (FH)**

Mother died at age 45 in automobile accident; Father, age 75, living and well. No siblings. One son, age 16, healthy. No known family history of heart disease, hypertension, or stroke. No known gout or renal stone. One grandparent known to have died of colon cancer at age 56.

### **Personal profile (PP)**

The patient lives with her husband, an insurance executive, and her 16-year-old high school student son in their own home in a local suburb. The family is financially stable. The patient enjoys her 40-50-hour work week as an editor for a business magazine. She is completing a master's degree in history and is planning to teach and write when this is completed. She has a few close friends; no family in the area. She enjoys walking and does 2-4 miles every day. Her diet is generally well balanced; she rarely drinks milk and does not take calcium nor antacids. She has a 30 pack, 1 year cigarette history and drinks, at most, 4-8 oz of wine a week if a social occasion presents itself. She has never used recreational drugs. She characterizes her life as pleasantly busy and stimulating. She is concerned because her current symptoms are making it difficult for her to enjoy her activities.

### **Review of systems (ROS)**

Other than items noted above, the ROS is essentially negative. Two years ago, the patient had a suspicious lesion excised from the bottom of her right foot, which was diagnosed as a complex nevus. No follow-up was recommended.

### **Menstrual and sexual history**

Periods continue at 28-30-day intervals; 3-4 days of moderate flow. There have been no changes. She is sexually active and monogamous with her husband. She has never been treated for a sexually transmitted disease. There has been some decrease in sexual activity over the past 3 months due to her fatigue. Patient's husband had a vasectomy 10 years ago, and she has not used supplemental birth control. Last pelvic examination and Pap smear were 6 months ago. Patient does not practice breast self-examination and has never had a mammogram.

There is no history of psychiatric disease or treatment.

### **Formulation of problem list from medical history**

#### **Active problems**

**Problem 1:** Fatigue

**Problem 2:** Low-grade fever  
foot, by

**Problem 3:** Back and flank pain history

**Problem 4:** Hypothyroidism, by history, under treatment

**Problem 5:** Hematuria x one, by history

**Problem 6:** Tobacco use, 30 pack/year history

#### **inactive problems**

**Problem 1:** Seasonal rhinorrhea

**Problem 2:** S/P excision complex nevus, right

### **Discussion of problem list**

#### **Active problems**

Problems 1, 2, and 3 are the major symptoms gleaned from the HPI. Since, it is not possible to define at this they are listed by symptom. Problem 5 also belongs to the

HPI. It is added as a piece of presumed historic data and requires verification **by the** clinician at the walk-in clinic since it may have bearing on the remainder of the HPI.

Problem 4, although not apparently contributing to the current symptoms, must be given a priority ranking, for data verification, for consideration in the course of any anticipated diagnostic or therapeutic intervention, and for the remote possibility that it may be related to the HPI. Because it is an ongoing problem, currently under *treatment*, it may logically be placed in the HPI as well as being considered active.

Problem 6, although likely not related to the HPI, certainly is a health concern for the patient, and at the very least demands some patient education intervention.

### **Inactive problems**

These are listed because of their potential for recurrence or for consideration in any long-term management of the patient. For example, should her present illness require long-term therapy, awareness of the seasonal rhinorrhea will remind the clinician to consider any potential drug interactions when the patient resumes her seasonal antihistamines. The complex nevus, though very likely a resolved problem, needs to be observed for recurrence and must be noted for the sake of comprehensiveness.

**Physical examination.** This is a well-developed, well-nourished white woman who appears anxious but not acutely distressed.

### **Vital signs**

**BP:** Both arms, sitting, 110/72 **Pulse**

**rate:** 110 and regular

**Temperature:** 100 degrees orally

**Respiratory rate:** 20/min

### **Skin**

Normal texture and turgor; color normal; no lesions noted except for well-healed surgical scar on sole of right foot

### **Lymph nodes**

Cervical, submandibular, supraclavicular, axillary, and inguinal not palpable

### **Head**

Normal hair distribution; no scalp lesions

### **Eyes**

Sclera and conjunctivae normal; no lid lag; fundoscopic examination normal bilaterally

### **Ears**

Normal hearing; TMs normal bilaterally

### **Nose and throat**

Entirely within normal limits (WNL)

### **Mouth**

Good dentition and hygiene; no oral masses or lesions seen

### **Neck**

**Supple** with full range of motion; thyroid nonpalpable without masses; trachea midline

**Chest and lungs**

normal respiratory excursion and diaphragmatic motion; vesicular breath sounds throughout; fremitus normal; no **sales** nor rhonchi heard; no tenderness to percussion over ribs, sternum, nor spine; mild costovertebral angle (CVA) **tenderness**, right

### **Breasts**

Symmetrical elevation of nipples without dimpling; mild bilateral cystic variants noted; no nipple secretion, masses, **no** tenderness

### **Cardiac**

PMI 5th intercostal space, 4 cm to left of midsternum; no heaves or thrills; A2 greater than P2 at base; S1 and S2 normal all positions; no S3 nor S4, no murmur or click heard; rhythm sinus tachycardia at 110/min

### **Vascular**

**All** pulses 2 + and equal throughout without bruit

### **abdomen**

scaphoid; RLQ surgical scar; no bruits heard; bowel sounds normal; liver percusses to 6 cm; liver and spleen not palpable; right flank examination reveals fullness with tenderness and a soft mass deep and easily palpable, approximately 3 X 4 cm; renal tip not clearly appreciated

**Muloskeletal** normal

### **Neurologic**

**Mental status:** Oriented x three

**I nerves (11-XII):** WNL

: DTRs 3 + and equal; no clonus; all muscle groups 4/5 and symmetrical; no Babinski elicited

Sensory: Vibration, pain, proprioception intact

Cerebellar: Grossly normal upper and lower

Gait and station: Normal; no tremor

Back

Full range of motion; normal lordosis; no spinal tenderness

Pelvic and rectal

Introitus normal; speculum examination reveals no abnormalities; on bimanual, the uterus is consistent ~Nitfreely mobile without mass or irregularity; both adnexae easily palpated and clear; ovaries normal in size anc ~s tender; rectovaginal examination confirms pelvic; no rectal masses; stool guaiac negative

### **Formulation of problem list from physical examination**

Active problems

inactive problems

Problem 7: Sinus tachycardia

Problem 3: S/P appendectomy

Problem 8: Right flank mass

### **Discussion of problem list**

On physical examination, two new problems have been observed, which were not apparent in the history: the presence of a sinus tachycardia and of a mass palpated in the right flank. These findings are added to the problem lee derived from the medical history. Also, although the history indicates appendectomy, this was neglected as an

addition to the inactive list earlier; it should now be added. (Why might this be an important bit of past medical history in this particular case?)

There now exists a list of problems presented by L.P., cited at the level to which they are absolutely understood. This problem list is the basis for hypothesizing a differential diagnosis, planning a diagnostic workup, and using the results of the expanded data base to synthesize and reorganize the primary problem list as the clinical problem-solving process is put into action.

## 111. APPROACH TO THE DIFFERENTIAL DIAGNOSIS

**A. Formulating hypotheses.** As clinicians obtain the medical history and do the physical examination, they consider, check, verify, and reject possible etiologies of the symptoms and signs encountered. Hypothesis formulation results in the list commonly known as the **differential diagnosis**, a composite of all of the possible etiologic bases for each of the problems that have been defined. The differential diagnosis remains speculative until one or more of the possibilities is proven to be the genesis of the problem. Clinicians must beware, however, of **premature closure**. Only hypotheses, not decisions, must be made until all of the information is collected.

**1. From the medical history.** From the time the patient first presents with a chief complaint (CC), the clinician should begin to think in terms of pathophysiology. If the symptoms are vague or general, or the interviewer has not yet learned much about disease process, it is best to use the **seven parameters** (see Chapter 3 I C 2) to obtain information without attempting hypotheses. The more the interviewer has learned about pathologic processes, the more refined his or her hypothesis formulation will be.

- a. A young runner who presents with a CC of "pain in the foot," leads the interviewer to consider the anatomic area and the pathologic processes that are common to that area in the settings of youth and running.
- b. A CC of "pain in the foot" from a sedentary 75-year-old man would direct the questioner quite differently. (The medical student is apt to make very primitive attempts to juggle these possibilities.)

**2. From the physical examination.** As the clinician moves to the physical examination, focus is guided by the information obtained in the history. If the patient's complaints are directed to the painful foot, the clinician will be more than usually meticulous about examining the area indicated. However, it is also necessary to consider **systemic disease** as the cause of a local symptom. If the examiner's level of knowledge precludes a clear-cut hypothesis derived from the history, he or she ought to approach the physical examination **generically**, by looking everywhere for clues. Hypothesis formulation should be used wisely, and premature closure should be avoided at all costs.

**B. Systems approach to differential diagnosis.** After creating a problem list, the clinician must derive a differential diagnosis, the first step in converting problems to plans for intervention.

1. Most clinicians, including the most experienced, resort to "the books" to construct a list of diagnostic possibilities, which is both rational and sufficiently comprehensive to guarantee an efficient and effective approach to problem-solving. This can be the most interesting stage of the diagnostic process, but it must be both **adequately inclusive** and **reasonably exclusive**. Such results are usually best accomplished by a systems approach.
  2. With the history, physical examination, and problem list, which constitute the primary data base, it is possible to proceed with the construction of a differential diagnosis, despite a limited understanding of the major body systems, which for the purposes of this discussion, include: skin, reticuloendothelial, cardiovascular, central and peripheral nervous, connective tissue, endocrine, gastrointestinal, musculoskeletal, renal-urinary, reproductive, respiratory, and psychiatric. Each clinician has a slightly different way of arranging a systems organization, but it is important that each has a defined method for constructing the differential diagnosis. **a. Systems.** The clinician now sorts through the above 12 systems, one by one, demanding
- 
- of each: Could any, several, or all of the problems be related to this system?

All possibilities  
should be listed.

**b. Categories of dysfunction.** The clinician should consider whether the system under scrutiny could be involved with one or more of the following pathophysiologic processes: congenital, degenerative, metabolic, infectious, immunologic, functional, toxic, or traumatic.

**c. Priorities.** Within each category of dysfunction, the priorities for further diagnostic and therapeutic inquiries should be determined.

**(1) Prevalence.** This is an issue of commonality in the general population.

How often may

one expect to see the dysfunction in the world at large? Are we dealing with mosquitoes or with zebras?

**(2) Probability.** How likely is it that this patient, of a particular age, sex, race, place of origin, and particular family and general health history, would have any of the categories of dysfunction listed?

**(3) Likelihood of poor outcome.** If the diagnosis is not made now, how will the patient be affected? Missing a fractured rib as a cause of chest pain is a far less ominous error than missing an early pneumococcal pneumonia.

### C. Generating a differential diagnosis from the problem list

1. The clinician should take each of the active problems in the problem list and construct a differential diagnosis based upon the information available. The following information should be gleaned for each problem:
  - a. The system from which this symptom or sign could arise
  - b. The category of dysfunction within each listed system that could account for the symptom or sign

- c. The priority of the dysfunction
2. To illustrate the application of the process, the first problem on the list generated for the case presented in Figure 10-1 will be worked through to a preliminary set of diagnostic possibilities in Figure 10-2.

## **Sample Case: Generating a Differential Diagnosis from the Problem List**

### **Problem 1: Fatigue**

#### **Systems**

In the instance of this ubiquitous and vague symptom, essentially every system must be considered as a potential source; therefore, it is prudent to move quickly to the second question.

#### **Category of dysfunction**

**Cardiovascular:** Primary organ failure (e.g., myocardial compromise due to either infectious, metabolic, endocrine, degenerative, immunologic, toxic, traumatic, or (remotely) congenital causes). From this survey of pathophysiologic possibilities, the following list is generated:

1. Myocarditis
2. Endocarditis
3. Amyloidosis
4. Hemachromatosis
5. Hypothyroid cardiomyopathy

#### **Figure 10-2. Continued.**

6. Ischemic heart disease
7. Connective tissue disease, lupus, or polyarteritis
8. Alcoholic cardiomyopathy

This list has already been narrowed by some of the information available, but it remains broad to be pared as the clinician moves forward in the decision-making process. This same process of listing is invoked foreach of the systems potentially implicated as a cause of fatigue.

#### **Priority**

In terms of **prevalence**, **probability**, and **potential for bad outcome** if not diagnosed or treated now, priorities for diagnosis and treatment must be established.

**Myocarditis** is sufficiently common to be considered. Also, in this particular patient there is a high-risk age, fever, and sinus tachycardia, all of which suggest myocarditis. Against this diagnosis is the duration of the symptom as well as its indolence.

**Endocarditis** is relatively common. Again there is fever and tachycardia plus a history of hematuria. The indolence is against the disease but does not rule it out. The absence of a murmur lessens the likelihood. The potential for fatal outcome in this treatable disease, however, makes it imperative that it remain on the list of considerations.

This same thought process should be applied to all of the cardiovascular possibilities until a reasonable assembly of primary considerations remains. The primary cardiovascular diseases to be put into the differential diagnostic list might rest at this level:

1. Subacute bacterial endocarditis
2. Viral myocarditis
3. Primary amyloidosis
4. Alcoholic cardiomyopathy
5. Cardiomyopathy of hypothyroidism
6. Idiopathic cardiomyopathy

Following the pattern set above for Problem 1, a full preliminary differential diagnosis scheme for this patient will be as follows:

### **Differential Diagnosis. Problem 1: Fatigue**

1. Subacute bacterial endocarditis
2. Viral myocarditis
3. Alcoholic cardiomyopathy
4. Cardiomyopathy of hypothyroidism
5. Idiopathic cardiomyopathy
6. Primary amyloidosis (very unlikely)
7. Connective tissue disease
8. Parenchymal renal disease, including nephrolithiasis with chronic pyelonephritis, glomerulonephritis, and toxic nephritis
9. Hypernephroma
10. Depression and anxiety
11. Substance abuse

The identical process is used to establish a differential diagnosis for each of the remaining active problems. As each problem is considered, a subset of recurrent diagnoses will emerge. Each time a diagnosis recurs, the probability of its being the genesis of the patient's present illness is increased. This reordering of probabilities will dictate the sequencing of the diagnostic procedures planned, and the list of differential diagnostic possibilities will, thus, be narrowed systematically and the workup more tightly focused. This is clinical problem-solving in action, based upon the two initial components of the data base: the medical history and the physical examination.

## **IV. FORMULATING A PLAN**

**A. From differential diagnosis to plan.** The plan develops from three basic determinations.

### **1. Additional information**

**a. In-depth history and physical examination.** Fleshing out details in the history and finetuning the physical examination are cost-effective and productive uses of the clinician's time. These steps should antedate elaborate laboratory tests, since they may narrow diagnostic possibilities and save the patient unnecessary interventions and expense. The clinician should:

- (1) Return to the bedside to clarify details and delve further into symptoms
- (2) Review preexisting medical records or laboratory data
- (3) Talk to prior caretakers who might shed light on the

problem (4) Confer with family members who may add important new information

**b. Consultation.** If consultation might preclude expensive or dangerous procedures or prompt necessary early therapy, it is appropriate to request that help now.

**c. Laboratory tests.** By looking at the differential diagnosis, the clinician can determine: (1) If preliminary laboratory tests would be helpful (2) Which tests could be done now (3) In what order will such tests best narrow the diagnostic field (see V for a detailed discussion of an approach to laboratory testing)

**d. Procedures.** It is important to determine which procedures need be done now to refine the diagnostic possibilities, to provide for the safety of the patient, or to guide emergency treatment before the data base is complete. The decisions about procedures must be made primarily in terms of the potential hazard to a patient if they are not done or are delayed; for example, the febrile, convulsing child with a stiff neck needs a lumbar puncture much more urgently than he or she needs a complete blood count (CBC) or a complete social history.

**2. Treatment.** Questions about early treatment must be asked even as the diagnostic workup is

considered. On occasion, both diagnosis and treatment must proceed simultaneously.

**a. Immediate interventions** apply in two instances:

- (1) **Life-threatening situations**, such as cardiac arrhythmia, tension pneumothorax, status epilepticus, or massive bleeding, when diagnosis of the underlying disease process is less urgent than treatment of the symptom or sign
- (2) **Patient comfort** when symptoms are so disabling to the patient that humane considerations demand symptomatic treatment without a definitive diagnosis

**b. Therapeutic trials**

- (1) Sometimes the institution of a therapeutic trial is prudent even while diagnostic workup is proceeding. For example, empiric antibiotic therapy can begin in a patient with a presumed infection while waiting 24-72 hours for results of cultures and sensitivities. This decision to institute therapy before arriving at a definitive diagnosis in the non-life-threatening situation is based upon the probability that therapy will alter the disease course before the pathology is labeled.
- (2) Therapeutic trial may be substituted for a definitive diagnostic procedure, when the diagnosis seems almost certain or the risks or costs of the test outweigh those of the therapeutic trial. For example, antihypertensive treatment can be instituted when a patient presents with symptoms and signs highly suggestive of the diagnosis without waiting for serum uric acid levels, which are suggestive, but not definitive. If the working diagnosis is correct, the patient will become asymptomatic quickly; if incorrect, no harm will have been done as long as the other diagnostic possibilities are pursued concurrently.

**c. Watchful waiting** is often the most difficult decision for the clinician, who is trained to intervene-to do something-and whose patient expects nothing less. Many of the problems with which patients present are self-limited, and prudent observation will allow time and "mother nature" to do theirwork. When the clinician has determined that "doing nothing" will not harm the patient, this approach should be strongly considered.

**3. Patient education.** Throughout the process of diagnosis and therapeutic interventions, a concern for the patient's queries and worries must be kept uppermost in the clinician's mind. It is the patient who comes with, and ultimately owns, the problem. He or she must be informed as decisions are made.

**a. Negotiating procedures**

(1) If the patient is conscious and aware, all interventions should be discussed before the

fact. Reasons for any diagnostic intervention should be shared with the patient.

(2) If there is hazard, discomfort, or expense to be incurred, the patient must not only be aware of, but agree to, what is planned.

**b. Communicating progress and prognosis.** Patients are often reluctant to ask questions because of lack of knowledge, fear of being considered nuisances, respect for the clinician's time, or fear of potential bad news. The patient should know as much as he wants to know and be encouraged to ask questions.

**B. Updating and revising the differential diagnosis.** As new information is acquired or as the patient's clinical condition evolves, the clinician repeatedly revises and alters the provisional differential diagnosis.

**1. Reviewing new information.** As new data from the laboratory, physical examination, or history are collected, thinking and planning must be adjusted accordingly.

**2. Assessing additional information needs**

**a.** When new data are added to the chart and consequent revisions are made in the problem list, differential diagnosis, or management plan, the need to confirm or add to the growing data base must be considered. The decision to request new information derives from answers already supplied or diagnostic possibilities that have been enhanced or negated.

**b.** A piece of information that does not fit the pattern must be either confirmed or rejected; for example:

(1) If a patient presents with a typical clinical history of pneumococcal pneumonia, has gram-positive diplococci in the sputum smear, but does not grow *Streptococcus pneumoniae* on culture, the clinician must reconsider the diagnosis.

(2) If the patient, now 36 hours into the appropriate regimen of penicillin, is afebrile and looking good, perhaps the negative sputum culture needs to be discounted.

(3) If the clinical response to the treatment for pneumococcal disease has been disappointing, the Gram stain may have been misinterpreted. Alternative diagnostic possibilities must be entertained.

**3. Eliminating disproven diagnoses.** When the primary diagnostic studies show definitive evidence that one of the differential diagnostic possibilities has been ruled out, the record should reflect this. Negative information is helpful in narrowing the differential diagnosis.

**4. Revising the problem list.** In the excitement of chasing the diagnosis, the problem list should not be forgotten. It is the problem list from which the progress notes are written and from which new diagnostic possibilities may be derived.

a. If it now appears that two or more problems are secondary to a single pathologic process, the record should be updated so that others caring for the patient can follow the progress of problem resolution.

b. If the patient reports new problems, they are added to the list.

c. If a problem changes or disappears, this is reflected in the problem list.

**5. Revising therapeutic plans.** Treatments may need to be stopped or altered if they:

a. Are not helping the patient

b. Are creating new problems

c. Become irrational in the face of new diagnostic evidence

d. Have succeeded in eliminating one or more of the problems or diagnostic possibilities

**6. Keeping the patient advised.** The patient should be informed of changes in plans or of new developments in the "case."

#### Figure

**C. The process of working from the differential diagnosis to a preliminary plan** is illustrated in Figure 10-3, using the sample case used in Figures 10-1 and 10-2.

### Sample Case: Working from the Differential Diagnosis to the Preliminary Plan

#### Problem 1: Fatigue

##### Subacute bacterial endocarditis

##### Further information from history and physical examination

1. Obtain history of any dental, GU, GI procedures, or IV drug use 2. Listen again for murmur

**Laboratory studies and procedures** 1. Blood cultures, CBC\* 2.

Echocardiogram\* **Therapy:** None now **Patient education** 1. Discuss laboratory tests 2. Discuss echocardiogram

##### Viral myocarditis

**Figure 10-3.** Continued.

**Further information from history and physical examination**

1. Check history for any antecedent viral illness  
2. Listen again for S3, quality of heart sounds

**Laboratory studies and procedures:** Echocardiogram\*

**Therapy:** None

**Patient education:** Discuss echocardiogram

**Cardiomyopathy of hypothyroidism**

**Further information from history and physical examination:** Get results of recent thyroid function tests  
**Laboratory studies, therapy, and patient education:** None

**Alcoholic cardiomyopathy**

**Further information from history and physical examination**

1. Question again regarding patient's alcohol intake  
2. Question family regarding patient's alcohol intake  
**Laboratory studies and procedures** 1.

Electrocardiogram (EKG)

2. Echocardiogram\*

3. Red cell indices, CBC\*

**Therapy:** None

**Patient education:** Discuss laboratory studies and reasons

**Idiopathic cardiomyopathy.** Covered in three possibilities discussed above under alcoholic cardiomyopathy  
**Connective tissue disease**

**Further information from history and physical examination**

1. ROS pertinent to connective tissue disease  
2. Recheck physical for signs of connective tissue disease  
**Laboratory studies and procedures** 1.

Antinuclear antibody (ANA)

2. Sedimentation rate

**Therapy and patient education:** As above

**Renal disease**

**Further information from history and physical examination**

1. Check with walk-in clinic regarding urinalysis  
2. Review analgesic history  
3.

Reassess right flank mass  
**Laboratory studies and procedures**

1. BUN, creatinine, serum calcium, phosphorus, uric acid, urine sediment, and urinalysis

2. Renal ultrasound or scan

**Therapy:** None

**Patient education:** Explain tests and procedures

**Depression and anxiety.** Low probability; hold for later consideration

**Substance abuse.** Review history; talk with family

**Differential diagnosis and plan revision based on the new information**

### Further information from history and physical examination

All additional data collected above is negative except for a positive history of a routine dental hygiene visit 3 weeks before onset of symptoms.

### Laboratory studies and procedures

1. CBC reveals a mild normochromic, normocytic anemia without an increase in WBCs.
2. All chemistries are normal.
3. EKG and echocardiogram are normal.
4. Blood cultures are negative at 48 hours.
5. Urinalysis is positive only for 10-15 RBCs/hpf.
6. Renal ultrasound reveals a solid mass, right kidney.

### New differential diagnosis. Problem 1: Fatigue

1. Hypernephroma
2. Subacute bacterial endocarditis (highly unlikely)

### Figure 10-3. Continued.

The procedure for evaluating the differential diagnosis for each of the remaining problems is the same. The data collected on this first run allow the student to consolidate and subsume problems, to narrow the differential diagnostic possibilities, and to make the next step in planning for any additional diagnostic or therapeutic steps. The process illustrated for formulation of the initial plan is repeated as often as necessary to arrive at a definitive diagnosis and management plan.

V. APPROACH TO CHOOSING A LABORATORY DATA BASE. This section gives an overview of the basic principles essential to the use of laboratory studies and commonly used tests in primary assessment. It is important to note that **this overview supplements, but does not replace, disease** specific reviews. The difference between screening asymptomatic individuals and the application of laboratory studies to problem lists and differential diagnoses are discussed. Some of the principles of test selection based on simple statistical analytical usefulness are reviewed and applied to the sample case (Figure 10-4).

### Figure 10-4.

#### Sample Case: Choosing Primary Laboratory Procedures

To illustrate the approach to choosing a primary laboratory data base for L.P., the differential diagnosis compiled in Figure 10-2 for Problem 1 (fatigue) should be reviewed. For each of the diagnostic considerations, the possible laboratory tests must be examined based upon their **sensitivity, specificity, and risk:benefit ratio.**

### Subacute bacterial endocarditis

#### CBC

1. Sensitivity is high for defining anemia, red cell morphology, and elevated WBC with
  - \*Note the recurrence of the same tests or procedures in more than one diagnostic consideration.

left shift, all of which are expected in any valvular disease with systemic infection.

2. **Specificity.** No abnormality on CBC is disease-specific but taken as a part of the total data base, the CBC will be useful in enhancing or reducing the possibility of this diagnosis.
3. **Risk:benefit ratio.** Low cost and low risk to the patient make this test worth doing at this time.

#### **Urinalysis**

1. **Sensitivity** is high for the detection of red blood cells.
2. **Specificity** is low, since red blood cells in the urine may mean any number of things.
3. **Risk:benefit ratio.** Since the test is inexpensive, without risk, and may add useful information to the data base, it is indicated.

#### **Electrolytes**

Since this ~~patient is alert and ambulatory and her condition is not metabolically~~ critical, there seems to be no need to do electrolytes. These tests have no useful sensitivity or specificity in terms of this differential diagnostic possibility.

#### **BUN and creatinine**

Neither specific nor sensitive in terms of endocarditis; therefore, they are not useful in this diagnostic consideration.

**Serum glucose** No indication

**Serum enzymes** No indication

**Cholesterol** No indication

#### **Bilirubin**

Since bilirubin might be elevated in the hemolytic process sometimes seen in subacute bacterial endocarditis, one might consider requesting this test. However, its specificity in the diagnosis considered is so limited that it does not seem indicated at this time.

#### **EKG**

This patient has an unexplained tachycardia, and primary cardiac disease is being considered. EKG will be very nonspecific in regards to this diagnostic possibility. As the workup progresses, the EKG may eventually become imperative.

#### **Chest x-ray**

This is a hard call. The sinus tachycardia raises the possibility of insipient cardiac failure, which the chest x-ray might help define. There is also the possibility of calcification, indicating underlying valvular abnormality, but the auscultatory examination does not suggest this. The chest x-ray cannot be expected to help much in refining this portion of the differential diagnosis.

After thinking through the potential yield of each of the laboratory studies considered, the plan for differential diagnostic possibility, **subacute bacterial endocarditis**, might include: CBC, urinalysis, and (possibly) EKG. Blood cultures and echocardiogram become necessary if clinical judgment indicates that bacterial endocarditis is the primary diagnostic consideration. However, perusal of the list and review of the physical examination findings indicate that **the flank mass is of a higher magnitude of concern**.

Before writing orders for primary laboratory testing for this patient, the clinician uses the above decision-making process for each of the remaining diagnostic considerations. A **composite list** of the **primary tests** most likely to lead to a diagnosis most quickly, efficiently, and with the minimum of risk and cost is made. Pending the results of these first tests, the clinician may now write the orders and enter the laboratory diagnostic plan in the patient's progress notes.

### **Problem 1: Fatigue**

#### **Assessment-strongest differential diagnostic**

**considerations** 1. Subacute bacterial endocarditis 2.

Hypernephroma

#### **Still to be ruled out**

1. Viral myocarditis
2. Alcoholic cardiomyopathy
3. Cardiomyopathy of hypothyroidism
4. Idiopathic cardiomyopathy
5. Primary amyloidosis
6. Connective tissue disease
7. Chronic renal disease
8. Depression and anxiety
9. Substance abuse

### **Plan.**

CBC, urinalysis, EKG, thyroid function studies, serum creatinine all ordered today. If indicated from EKG, will plan echocardiogram for this afternoon. Renal ultrasound scheduled for tomorrow A.M. Family conference regarding substance abuse and any indications of emotional or behavioral changes is scheduled for tonight.

### **Summary**

Renal ultrasonography revealed a solid mass in the upper pole of the right kidney. Surgical exploration confirmed hypernephroma, which could account for the fatigue as well as the physical examination findings in the abdomen and the abnormal laboratory values. Sinus tachycardia and low-grade fever disappeared after recovery from the nephrectomy performed.

## **B. Symptom-related laboratory examinations**

1. **Choosing the appropriate tests.** Before ordering a laboratory test, the clinician should determine the following:

**a. Cost-effectiveness.** Is this test the cheapest way in time, money, and risk to the patient

to get the diagnostic answers to serve the patient best?

**b. Diagnostic effectiveness.** Is this test sufficiently **specific** and **sensitive** to be indicated at this time?

**(1) Specificity.** The percent of time that a positive test result correctly indicates that the

patient does have the disease in question. A specificity of 90% means that there will

be 10 false-positives per 100 patients tested.

**(2) Sensitivity.** The percent of time that, when the test is negative, the disease is not

present. A sensitivity of 95% means that there will be 5 false-negatives for every 100

patients who actually have the disease for which they are being tested.

**c. Risk:benefit ratio.** Is this test sufficiently sensitive to be helpful in the indication of the presence of the disease being considered, and at the same time, sufficiently specific to preclude a futile chase, so that the risk of the test to the patient can be justified? For example:

**(1)** Sending a blood sample to the laboratory for a hemoglobin determination when the

diagnosis of anemia is being considered is highly sensitive, highly specific, of relatively

low cost, and of no risk to the patient.

**(2)** Careful consideration must be given to doing a coronary arteriogram on a patient

whose condition precludes surgery even if a lesion is found and for whom the physical

risk of the test is high.

**2. Effective use of laboratory data.** If the laboratory result does not come out as predicted, the clinician must then decide whether or not the unexpected result warrants a **repeat test for confirmation, relegation to the "red herring" or "fluke" category**, or a **new investigative quest**. For example, if the CBC ordered on the patient expected to be anemic reveals a normal hemoglobin and hematocrit, but a very low white count, what does this do to the differential diagnosis and the next diagnostic step? If the anemia is still thought to be present, should the test be repeated, or should the health care team abandon the diagnosis of anemia and pursue the low white blood cell count?

**C. Common laboratory procedures.** This section is intended to be a review of common and frequently ordered tests as an illustration of general principles. For disease-specific indications and interpretations of these tests, the reader is referred to any standard textbook of medicine.

1. **CBC.** The CBC usually includes the **hemoglobin, hematocrit, red cell indices, white blood cell count with differential**, and an estimate of the **platelet count**. This is a relatively inexpensive, fully automated test (except for the differential count) with high specificity, sensitivity, and accuracy for the diagnosis of anemia, differentiation of large categories of anemia (e.g., micro-, normo-, and macrocytic anemias), and suggestion as to quantitative and qualitative abnormalities of white blood cells and platelets.
2. **Urinalysis.** The urinalysis may be ordered as a part of the routine **assessment of undifferentiated disease, to test diagnostic hypotheses**, or as a **follow-up in therapy**. Of most importance to the student of introductory clinical medicine is an understanding of the components of the test and their clinical usefulness.
  - a. **Specific gravity** (usual range *1.010-1.035*). This is an indirect measure of the kidney's ability to conserve or to dump body water and solute. False elevations of the specific gravity may occur with massive loads of solute, such as glucose or protein.
  - b. **Protein, sugar, ketones, blood, and pH.** All are quickly tested by means of impregnated paper or "dipstick."
  - c. **Appearance.** Color and turbidity are noted by visual inspection.
  - d. **Sediment.** Cellular components and bacteria in the stained or unstained sediment indicate specific functional processes.
3. **Serum chemistries.** This group of tests, often grouped into panels, is probably one of the most useful, and yet most often abused, group of laboratory examinations available. There is a tendency to order a full panel without regard for the questions being asked about the patient's particular problem.
  - a. **Electrolytes [i.e., sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>), and chloride (Cl<sup>-</sup>)]**. The role of the clinician is to determine from the list of problems and differential diagnostic possibilities whether any or all of the above chemistries will lead to a diagnostic resolution and a therapeutic plan. Serum electrolytes are highly specific and sensitive in a properly considered clinical situation but should be ordered with a particular question in mind.
  - b. **Creatinine and blood urea nitrogen (BUN).** These are the two standard serum assessments of renal function.
    - (1) **Creatinine** becomes elevated when the renal clearance drops below approximately one quarter of its normal capacity. The elevation of creatinine warrants investigation of the specific functional problems: circulatory impairment (prerenal), primary kidney failure (renal), or urinary tract obstruction (postrenal).
    - (2) **BUN** is a less specific test for renal impairment as it may be elevated as a result of excessive absorption of urea nitrogen into the circulatory system, as well as from the inability of a diseased kidney to excrete urea.
  - c. **Serum glucose.** This is a highly specific and sensitive test for **metabolic failure to handle carbohydrates**. The significance of an abnormal serum glucose must be

interpreted in light of the metabolic status of the patient.

- (1) Elevation of fasting blood glucose levels usually indicates the presence of diabetes mellitus or glucose intolerance.
- (2) Low levels are more difficult to interpret but could suggest an insulin-secreting tumor or the excessive use of exogenous insulin.

**d. Serum enzymes.** These tests are used to **verify or eliminate the probability of specific organ damage**, usually toxic, infectious, or ischemic. Students should be acquainted with the specificity of the various enzyme analyses and their usefulness in the diagnosis of liver, cardiac, bone, pancreatic, and muscle disease. The circumstances under which **falsepositivity** occurs in these tests must be understood and taken into consideration when ordering them and using them to make diagnostic decisions.

**e. Serum cholesterol** (see V A c)

**f. Serum bilirubin.** This determination is useful in the consideration of either primary liver disease, extrahepatic biliary obstruction, or hemolytic disease.

**4. Electrocardiogram (EKG or ECG).** The decision to order an EKG presents one of the commonest dilemmas in choosing tests. Because it is harmless and "noninvasive," the tendency is to proceed at the most minimal provocation. The EKG, when fully processed, is a test that will cost the patient or his third-party payer between \$75 and \$100. This is a small price if the test is helpful in managing the patient's problems but not if it is ordered without specific purpose. The student should have a working knowledge of the electrophysiology basic to the interpretation of the test, the skill to apply the electrodes and record a 12-lead EKG, and a preliminary approach to "reading" the EKG. Minimally, he or she should know how to determine rate and rhythm, electrical axis, P-wave morphology, P-R interval, QRS interval, Q-T interval, QRS morphology, S-T segment position, and T-wave morphology.

a. Because of its broad applicability in defining cardiac dysfunction, the EKG will likely be

indicated in any patient in whom cardiac disease is considered.

b. The test is also quite sensitive for detecting electrolyte abnormalities, although serum de

terminations of the electrolyte in question are much more specific.

c. There are toxins and drug overdoses for which the EKG is crucial in following the patient

for dangerous conduction problems.

d. Certain metabolic and endocrine crises require the EKG as part of progress monitoring.

**5. Chest x-ray.** The chest film is one of the commonest laboratory procedures ordered. It is a noninvasive, safe, but relatively expensive (approximately \$100) test. Like the EKG, it has a wide range of applicability in the evaluation of a patient suspected of having primary lung disease, lung disease secondary to cardiac failure, mediastinal disease, or less commonly, lung involvement in systemic or remote organ pathology.

## STUDY QUESTIONS

**Directions:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. A 63-year-old white man comes in with a CC of "pain in the right calf when walking." The pain is always immediately relieved by rest.

All of the items below should be recorded as active problems EXCEPT

- (A) a 60 pack/year smoking history
- (B) a serum cholesterol of 330 mg/100 ml (6 months ago)
- (C) appendectomy at age 22
- (D) FH of young cardiac deaths
- (E) diet-controlled diabetes mellitus

2. The clinician is asked to evaluate a 24-year-old man for a bus driver's license application. Which one of the following historic items should be entered as Problem 1 ?

- (A) Broken leg at age 16
- (B) Jail sentence for marijuana possession at age 19
- (C) Myopia (nearsightedness) sufficient to require glasses
- (D) Strong FH of diabetes mellitus
- (E) History of rejection from the armed forces because of an inguinal hernia

3. In the problem-oriented medical record, a problem listing of inactive should be made for any problem that

- (A) requires further data collection now
- (B) is of no importance to patient care
- (C) is quiescent but of potential future significance
- (D) is of historic interest only
- (E) is of doubtful validity

4. A 77-year-old woman comes into the emergency room with a CC of "dizziness." Which one of the following problems should be relegated to the inactive list?

- (A) high blood pressure for 20 years
- (B) insufficient income to buy adequate food
- (C) rapidly progressive unilateral hearing loss for the last 6 months
- (D) cholecystectomy 4 years ago
- (E) aortic valve replacement 2 years ago

5. All of the following statements about Pap smears of the uterine cervix are true EXCEPT

- (A) the sample is considered inadequate if endocervical cells are not present
- (B) annual Pap smear screening should begin for all women at age 16
- (C) human papilloma virus infection may predispose to premalignant changes in the cervical cells on Pap smear
- (D) a history of multiple sexual partners increases the risk of cervical malignancy
- (E) after age 60, the frequency of Pap smear screening may safely be reduced to every 3-5 years

6. Each of the following parameters is critical in choosing any given laboratory test EXCEPT

- (A) specificity of the test
- (B) sensitivity of the test
- (C) cost:benefit ratio of the test
- (D) on site availability of the test
- (E) patient willingness to undergo the test

7. The CBC is highly specific for each of the following abnormalities EXCEPT

- (A) anemia
- (B) polycythemia
- (C) thrombocytosis
- (D) leukopenia
- (E) leukocytosis

8. The routine urinalysis (i.e., dipstick plus microscopic examination of the spun urine sediment) is highly sensitive for establishing the presence of each of the following conditions EXCEPT

- (A) hematuria ( B ) pyuria
- (C) albuminuria
- (D) cancer of the kidney
- ( E ) acute glomerulonephritis

**Directions:** Each item below contains four suggested answers of which **one or more** is correct. Choose the answer

**A** if **1, 2, and 3** are correct

**B** if **1 and 3** are correct **C** if **2 and 4**  
are correct

**D** if 4 is correct

**E** if **1, 2, 3, and 4** are correct

9. In the problem-oriented medical record, an active problem is defined as one which requires

- (1) therapeutic action
- (2) diagnostic action
- (3) revision and update
- (4) patient education action

**Directions:** The groups of questions below consist of lettered choices followed by several numbered items. For each numbered item select the **one** lettered choice with which it is **most** closely associated. Each lettered choice may be used once, more than once, or not at all.

### Questions 10-14

For each age-group listed below, select the laboratory test that is most appropriate for screening asymptomatic patients.

- (A) Serum cholesterol ( B ) Annual EKG
- (C) No routine laboratory screen recommended (D) Annual CBC and urinalysis (E) None of the above

10. Children from infancy to 2 years of age 11. Men from 10-20 years of age 12. Individuals from 20-40 years of age 13. Women from 40-60 years of age 14. Individuals over 75 years of age

### Questions 15-19

For each of the case scenarios presented below, select the most likely diagnosis based upon prevalence in the population at large and probability in the individual case.

- (A) *Neisseria gonorrhoeae* infection
- ( B ) *Candida albicans* infection (C) *Chlamydia* infection
- (D) Human immunodeficiency virus infection (E) None of the above

15. Asexually inactive 26-year-old woman with a 5-day history of a thick, curdy white, vaginal discharge and vulvar itching
16. A 26-year-old man with a thick, yellow, penile discharge who had a single sexual encounter with a prostitute 5 days ago
17. A 30-year-old intravenous heroin user who comes in with generalized lymphadenopathy
18. A 65-year-old widow who comes in with a history of vulvar itching without discharge
19. A 23-year-old sexually active woman who is asymptomatic but is found on pelvic examination to have a purulent cervicitis

## ANSWERS AND EXPLANATIONS

**1. The answer is C.** [11 A 1-3] Rational thought would dictate that the appendectomy 41 years ago has no relationship to the presenting complaint; however, since it represents the historic absence of an organ, it deserves to be included on the inactive list. The smoking history, elevated cholesterol, FH of cardiac events, and the presence of diabetes in this patient all constitute risk factors for vascular disease. Combined with the classic history for intermittent claudication, these vascular risk factors are prominent considerations in this patient's active problem list and may be directly related to the CC.

**2. The answer is C.** [11 B, C] Since the task at hand is to determine this man's physical ability to drive a public conveyance, the primary concern is his vision. The presence of myopia and the need for glasses are paramount and should

constitute the most important problem related to the task. The broken leg belongs on an inactive list; the history of marijuana use must be included but is of less significance today than is the myopia. The FH of diabetes is important to long-term care but is irrelevant to the bus driver's license as long as the candidate is not symptomatic. The inguinal hernia has importance to the patient but none to the bus company.

**3. The answer is C.** [II C2] In formulating the inactive problem list, the clinician is concerned with a data base that can be used to guide current and future patient care. Therefore, even a past medical problem, now apparently resolved but with the potential of resurfacing or later creating confusion, must be recorded. By definition, there is no need to pursue further information at this time. Although the problem may be irrelevant to the HPI, it may be relevant to the long-term comprehensive care of the patient. Validity is not a priority issue for inactive problems.

**4. The answer is D.** [I/ C2] The history of gallbladder removal 4 years ago is unimportant to the presenting problem, although it must be noted for the record in the event of future abdominal complaints. Any one of the four remaining problems listed could be implicated in the current problem. Uncontrolled high blood pressure may be associated with dizziness; cerebral vasoconstrictive or occlusive events, leading to vestibular dysfunction, may be secondary to hypertensive cerebrovascular abnormalities. Poor diet may lead to anemia or specific nutrient deficiencies, which could result in dizziness. The presence of unilateral hearing loss must be evaluated for the possibility of inner ear disease or eighth nerve tumor as the basis for the presenting complaint. Dizziness is a common symptom of aortic valve disease or prosthesis dysfunction.

**5. The answer is B.** [VA 3 a] There is no evidence to support the need for routine Pap smears in adolescents based on age. The time to begin this screen is with the onset of sexual activity, in the rare instance of vaginal symptoms, or with a history of DES exposure. Most cytologists worry that sampling is inadequate if endocervical cells are not present. There is good evidence now to indicate that women infected with the human papilloma virus have an increased risk for carcinoma in situ, as well as a more rapid progression from the dysplastic stage to carcinoma in situ. There is a significant correlation between number of sexual partners and early age of sexual activity with dysplasia and carcinoma in situ on Pap smear. The incidence of carcinoma of the cervix drops precipitously after menopause, leading most clinicians to reduce the frequency of Pap smears after age 60.

**6. The answer is D.** [V B 1] If a test is specific and sensitive for the diagnosis being considered, if it has a positive cost:benefit ratio, and the patient is willing to undergo the test, the basic criteria for the need for the test have been met. Once

the test has met these criteria, the place where the test may be done becomes a nuisance factor but it does not justify abandoning it.

**7. The answer is C. [V C 1]** A rough estimate of platelets may be made from the stained blood smear; however, the diagnosis of thrombocytosis requires a full platelet count, which is not a part of the standard CBC and must be ordered as a separate test. Anemia is diagnosed definitively by a reduction in hematocrit, hemoglobin, or total red cell count—all of which are a part of the CBC. Polycythemia (too many red blood cells) is also specified in this test, as are leukopenia (too few white blood cells) and leukocytosis (too many white blood cells). The numerical standards of normal ranges for each of the above have been well established and are accurately assessed in the CBC with the noted exception of the platelet count.

**8. The answer is D. [V C 2]** Cancer of the kidney cannot be diagnosed by urinalysis. The urine in this disease may vary from completely normal (usual) to revealing the cancer cells (rare). Thus, the test is never sensitive and is rarely specific for the diagnosis. In contrast, hematuria (blood in the urine), pyuria (white blood cells in the urine), albuminuria (albumin in the urine) are straightforward observations; they are not.

## COMPREHENSIVE EXAM

### STUDY QUESTIONS

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### LITERATURE

1. J. L. Willms, J. Lewis "INTRODUCTION TO CLINICAL MEDICINE" National Medical Series from Williams&Wilkins, 1991, 260 P.
2. MOSBY'S Medical Encyclopedia. The Learning company, 1997/
3. Mark Manual. Internet Edition.
4. Wikipedia. The Free Encyclopedia.