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Rapid Review PATHOLOGY

Fourth Edition

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RAPID REVIEW PATHOLOGY

FOURTH EDITION

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To all our grandchildren—Austin, Bailey, Colby, Dylan, Gabriel, Phin, Rigney, Sofia, and those great-grandchildren yet to come—thank you for keeping us "young at heart."

—Nannie and Poppie

Preface

Writing a new edition of a book always provides an opportunity to improve upon previous editions. This fourth edition of *Rapid Review Pathology* reflects these improvements thanks to many discussions I have had over the past 4 years with my colleagues in the basic sciences and my students, and comments from students in other medical schools. The most substantial changes in this new edition include a new chapter entitled "Diagnostic Testing," more images, updated management of key diseases, more integration with the basic and clinical sciences, and more tables to summarize information, particularly in microbiology.

To users of the last edition of the book (*Rapid Review Pathology Revised Reprint,* Third Edition), a list of corrections and additions is available on your Student Consult page in the electronic version of *Rapid Review Pathology,* under the *Extras* tab. For instructions on how to activate your Student Consult version, see the PIN page on the inside front cover of your book and go to www.studentconsult.com to activate your PIN.

Edward F. Goljan, MD

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Acknowledgments

The fourth edition of *Rapid Review Pathology* has been extensively revised to provide students with even more high-yield information and photographs than in previous editions. Many of the photographs are grouped together in collages to provide students with an opportunity to quickly review infectious diseases, dermatology, hematology, endocrinology, and many other key areas. In addition, the emphasis on margin notes and increased content in the summary tables provides the student with a "rapid review" of high-yield material for pathology examinations and USMLE and COMLEX Step 1 and 2 examinations.

As in previous editions, I especially want to thank Ivan Damjanov, MD, PhD, whose many excellent photographs have been utilized throughout the book. I highly recommend his recently published Elsevier book, *Pathophysiology,* as a companion text to the *Rapid Review Pathology* text for providing students with an even greater understanding of pathophysiologic processes in disease. I also thank Edward Klatt, MD, who graciously allowed the use of so many of his excellent images from *Robbins and Cotran Atlas of Pathology,* a resource that I also highly recommend as a source of high-quality images and supplementary learning.

Special thanks to Nicole DiCicco and Christine Abshire from Elsevier, who kept track of all the major changes in the third edition and helped facilitate the early publication of the book. Special thanks also to Karlis Sloka, DO, valued friend and teacher, whose understanding of disease processes helped me throughout the entire writing of the new edition. I want to thank Jim Merritt, Senior Content Strategist of Medical Education, who is the inspiration and primary energy behind the entire Rapid Review Series. Thanks Jim for a job well done! Finally, I would like to thank the myriad of medical students who have sent me e-mails with encouraging words on how the book has helped them not only perform well on boards, but also become better doctors. In particular, I would like to thank Gabriel Tonkin, who sent me referenced and updated material on numerous subjects that I used throughout the writing of the fourth edition.

Edward F. Goljan, MD
"Poppie"

Contents

CHAPTER

1 Diagnostic Testing

I. Purpose of Laboratory Tests

A. Screen for disease

1. General criteria for screening
   a. Effective therapy that is safe and inexpensive must be available.
   b. Disease must have a high enough prevalence to justify the expense.
   c. Disease should be detectable before symptoms surface in the patient.
   d. Test must not have many false positives (people misclassified as having disease).
   e. Test must have extremely high sensitivity.

Criteria for screening test: ↑sensitivity and prevalence; cost-effective; treatable

2. Examples of screening tests
   a. Newborn screening for inborn errors of metabolism
      - Examples—phenylketonuria, galactosemia, congenital hypothyroidism, and maple syrup urine disease
   b. Adult screening tests
      (1) Mammography for breast cancer
      (2) Cervical Papanicolaou (Pap) smear for cervical cancer
      (3) Screen for human papillomavirus DNA
      (4) Colonoscopy to detect/remove precancerous polyps
      (5) Fecal occult blood testing to detect colon cancer
      (6) Prostate-specific antigen (PSA) to detect prostate cancer
         - Currently, there is debate over the usefulness of this test.
      (7) Bone densitometry scans to detect osteoporosis in women
      (8) Fasting lipid profiles to evaluate coronary artery risk
         - Includes total cholesterol, high-density–lipoprotein cholesterol, low-density lipoprotein, and total triglyceride
      (9) Fasting blood glucose or 2-hour oral glucose tolerance test to screen for diabetes mellitus

Cervical Pap: overall best screening test for cancer

   c. Screening people with symptoms of a disease
      - Example—serum antinuclear antibody test to rule out autoimmune disease

B. Confirm disease; examples:

1. Anti-Smith and double-stranded DNA antibodies to confirm systemic lupus erythematosus
2. Chest x-ray to confirm pneumonia
3. Urine culture to confirm a urinary tract infection
4. Serum troponins I and T to confirm an acute myocardial infarction (AMI)
5. Tissue biopsy to confirm cancer
6. Fluorescent treponemal antibody absorption test to confirm syphilis

Confirm disease: serum troponins to diagnose AMI

C. Monitor disease status; examples:

1. Hemoglobin (Hb) A_{1c} to evaluate long-term glycemic control in diabetics
2. International normalized ratio (INR) to monitor warfarin therapy (anticoagulation)
3. Therapeutic drug monitoring to ensure drug levels are in the optimal range
4. Pulse oximeter to monitor oxygen saturation during anesthesia, asthmatic attacks

Monitor disease: HbA_{1c}, INR, pulse oximeter

Test result	Disease	No disease
+ Test	True positive(TP)	False positive (FP)
– Test	False negative (FN)	True negative (TN)

1-1: People with disease either have true positive (TP) or false negative (FN) test results. People without disease either have true negative (TN) or false positive (FP) test results.

II. Operating Characteristics of Laboratory Tests

A. Terms for test results for people with a specific disease (Fig. 1-1)

1. True positive (TP)
   - Definition—number of people with a specific disease who have a positive test result
2. False negative (FN)
   - Definition—number of people with a specific disease who have a negative test result

Test results in people with disease: TP and FN

B. Terms for test results for people without disease (see Fig. 1-1)

1. True negative (TN)
   - Definition—number of people *without* disease who have a negative test result
2. False positive (FP)
   - Definition—number of people *without* disease who have a positive test result

Test results in people without disease: TN and FP

C. Sensitivity of a test

1. Sensitivity of a test is obtained by performing the test on people that are known to have the specific disease for which the test is intended (e.g., systemic lupus erythematosus [SLE]).
2. Definition—likelihood that a person with disease will have a positive test result
3. Formula for calculating sensitivity is TP ÷ (TP + FN).
   - The FN rate determines the test's sensitivity.
4. Usefulness of a test with 100% sensitivity (no FNs)
   a. Normal test result *excludes* disease (must be a TN).
   b. Positive test result *includes* all people with disease.
      (1) Positive test result does *not* confirm disease.
      (2) Positive test result could be a TP or a FP.
   c. Tests with 100% sensitivity are primarily used to screen for disease.

Sensitivity = TP ÷ (TP + FN); "positivity" in disease

Test with 100% sensitivity: normal result TN; positive result TP or FP

D. Specificity of a test

1. Specificity of a test is obtained by performing the test on people who do *not* have the specific disease for which the test is intended.
   - Control group should include people of various ages and both sexes, and those who have diseases that are closely related to the disease for which the test is intended.
2. Definition—likelihood that a person *without* disease will have a negative test result
3. Formula for calculating specificity is TN ÷ (TN + FP).
   - FP rate determines the test's specificity.
4. Usefulness for a test with 100% specificity (no FPs)
   a. Positive test result *confirms* disease (must be a TP).
   b. Negative test result does *not* exclude disease, because a test result could be a TN or a FN.

Specificity = TN ÷ (TN + FP); "negativity" in health

Test with 100% specificity: positive test TP; negative test TN or FN

E. Comments on using tests with high sensitivity and specificity

1. When a test with 100% sensitivity (or close to it) returns negative (normal) on a patient on one or more occasion, the disease can be *excluded* from the differential list.
   - For example, if the serum antinuclear antibody (ANA) test returns negative on more than one occasion, the diagnosis of SLE can be excluded.

Usefulness of test with 100% sensitivity: exclude disease when test returns normal

2. When a test with 100% sensitivity returns positive on a patient, a test with 100% specificity (or close to it) should be used to decide if the test result was a TP or a FP.
   a. For example if the serum ANA returns positive in a patient who is suspected of having SLE, the serum anti-Smith (Sm) and anti–double-stranded DNA test should be used because they both have extremely high specificity for diagnosing SLE.
   b. If either or both tests return positive, the patient has SLE.
   c. If both tests consistently return negative, the patient most likely does *not* have SLE but some other closely related disease.

Usefulness of test with 100% specificity: distinguish TP from FP test result

III. Predictive Value of Positive and Negative Test Results

A. Predictive value of a negative test result (PV–)

1. Definition—likelihood that a negative test result is a TN rather than a FN
2. Formula for calculating PV– is TN ÷ (TN + FN).
   - PV– best reflects the true FN rate of a test.

Prevalence of disease	PV–	PV+
Low prevalence of disease	Increases (TN > FN)	Decreases (FP > TP)
High prevalence of disease	Decreases (FN > TN)	Increases (TP > FP)

1-2: Note that in a low prevalence situation (e.g., ambulatory population), the PV– increases, while the PV+ decreases. The reverse occurs in a high prevalence situation (e.g., cardiac clinic) in that the PV– decreases and the PV+ increases.

3. Tests with 100% sensitivity (no FNs) always have a PV– of 100%.
   - Disease is *excluded* from the differential list.

Sensitivity 100% → PV– 100% → excludes disease

B. Predictive value of a positive test result (PV+)

1. Definition—likelihood that a positive test result is a TP rather than a FP
2. Formula for calculating PV+ is TP ÷ (TP + FP).
   - PV+ best reflects the true FP rate of a test.
3. Tests with 100% specificity (no FPs) always have a PV+ of 100%.
   - Disease is *confirmed*.

Specificity 100% → PV+ 100% → confirms disease

C. Effect of prevalence on PV– and PV+

1. Definition—total number of people with disease in the population under study
   - Population includes people *with* disease and people *without* disease.

Prevalence: total # people with disease in a population

2. To calculate prevalence, people with disease are in the numerator (TP + FN) and people with disease (TP + FN) and without disease (TN + FP) are in the denominator.
   - (TP + FN) ÷ (TP + FN + TN + FP)

Prevalence: (TP + FN) ÷ (TP + FN + TN + FP)

3. Low prevalence of disease (e.g., ambulatory population) (Figs. 1-2 and 1-3)
   a. PV– increases because more TNs are present than FNs.
   b. PV+ decreases because more FPs are present than TPs.

↓Prevalence of disease: ↑PV–, ↓PV+

4. High prevalence of disease (e.g., cardiac clinic) (see Figs. 1-2 and 1-3)
   a. PV– decreases because more FNs are present than TNs.
   b. PV+ increases because more TPs are present than FPs.

↑Prevalence of disease: ↓PV–, ↑PV+

IV. Creating Highly Sensitive and Specific Tests

A. Ideal test (Fig. 1-4A)

1. Ideal test has 100% sensitivity (PV– 100%) and 100% specificity (PV+ 100%).
2. Note in the schematic that there are no FNs or FPs, because there is no overlap between the normal and disease population.
3. Ideal test is nonexistent; however, there are some tests that have very high sensitivity and specificity that come close to being the ideal test (e.g., serum levels of troponins I and T in diagnosing an AMI).

Serum troponins: ↑sensitivity and specificity; screen/confirm AMI

4. Most normal ranges (reference intervals) do *not* distinguish the normal from the disease population (see Fig. 1-4B and C).
   - Note that there is an overlap between the normal and the disease population in parts B and C of Figure 1-4.

B. Establishing a test with 100% sensitivity and PV– (see Fig. 1-4B)

1. To establish a test with 100% sensitivity and PV–, set the cutoff point for the reference interval at the *beginning* of the disease curve *(A)*.
   a. Note that this creates a test with 100% sensitivity and 100% PV–, because there are no FNs within the newly established reference interval (0 to A).
   b. Test can now be used to screen for disease.

↑Sensitivity/PV–: put cutoff point at the beginning of the disease curve; no FNs

2. Note that by increasing sensitivity there is *always* a corresponding decrease in the specificity and PV+ due to a greater number of FPs.

C. Establishing a test with 100% specificity and PV+ (see Fig. 1-4C)

1. To establish a test with 100% specificity/PV+, set the upper cutoff point for the reference interval at the *end* of the normal curve *(B)*.
   a. Note that this creates a test with 100% specificity and 100% PV+, because there are no FPs outside the reference interval (0 to B).
   b. Test can now be used to confirm disease.

↑Specificity/PV+: put cutoff point at the end of the normal curve; no FPs

2. Note that by increasing specificity there is *always* a corresponding decrease in sensitivity and PV–, due to a greater number of FNs.

V. Variables Affecting Laboratory Test Results

A. Premature newborns

1. Variable hemoglobin (Hb) concentration depending on the gestational age

此为试读，需要完整PDF请访问：www.ertongbook.com

A. Effect of low prevalence of systemic lupus erythematosus (SLE) on PV– and PV+

Sensitivity of serum ANA for SLE 100%
Specificity of serum ANA for SLE 80%
Prevalence of SLE is 1%
Population under study 1000

Number of people with SLE = 1000 x 0.01 = 10 x 100% sensitivity → 10 True positive (TP)
→ 0 False negative (FN)

Number of people without SLE = 990 x 80% specificity → 792 True negative (TN)
→ 198 False positive (FP)

	SLE	Control group
Positive test result	10 TP	198 FP
Negative test result	0 FN	792 TN
Total number	10	990

PV+ = 10 (TP) ÷ [10 (TP) + 198 (FP)] = ~ 5% (100 – 5 = 95% FP rate)
PV– = 792 (TN) ÷ [792 (TN) + 0 (FN)] = 100% (100 – 0 = 100% FN rate)

B. Effect of high prevalence of systemic lupus erythematosus (SLE) on PV– and PV+

Sensitivity of serum ANA for SLE 100%
Specificity of serum ANA for SLE 80%
Prevalence of SLE is 50%
Population under study 1000

Number of people with SLE = 1000 x 0.50 = 500 x 100% sensitivity → 500 True positive (TP)
→ 0 False negative (FN)

Number of people without SLE = 500 x 80% specificity → 400 True negative (TN)
→ 100 False positive (FP)

	SLE	Control group
Positive test result	500 TP	100 FP
Negative test result	0 FN	400 TN
Total number	500	500

PV+ = 500 (TP) ÷ [500 (TP) + 100 (FP)] = ~ 83% (100 – 83 = 17% FP rate)
PV– = 400 (TN) ÷ [400 (TN) + 0 (FN)] = 100% (100 – 0 = 100% FN rate)

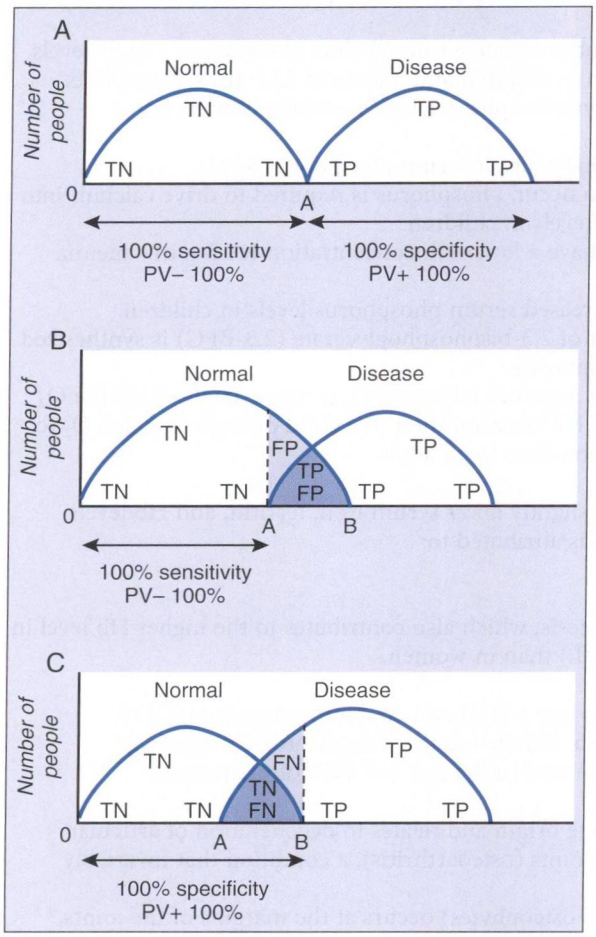
1-3: Note how the PV– remained the same in both prevalence situations because of the 100% sensitivity of the serum antinuclear antibody (ANA) for systemic lupus erythematosus (SLE). However, the PV+ significantly changed, going from a low prevalence of SLE (~5%) to a high prevalence of SLE (~83%).

Anemia prematurity: loss of iron from mother; blood loss from venipuncture

2. Anemia in prematurity is due to:
   a. Iron deficiency, related to loss of the daily supply of iron from the mother's iron stores
   b. Blood loss from excessive venipunctures in the premature newborn

B. Newborns

1. Newborns have higher normal ranges for Hb, Hct, and RBC counts than do infants and children.
2. HbF ($2\alpha/2\gamma$ globin chains) shifts the OBC to the left causing the release of EPO.
   - EPO causes an increase in Hb, Hct, and the RBC count.
3. Over the ensuing 8 to 12 weeks after birth, the Hb drops from 16.8 g/dL (range 14–20 g/dL) to 11 g/dL (this is called physiologic anemia).



1-4: Establishing tests with 100% sensitivity and specificity. Schematic **A** shows an ideal test with 100% sensitivity (100% PV–) and 100% specificity (100% PV+) when the normal range is 0 to *A*. Test results below the *A* cutoff point are all true negatives (*TN*), whereas those beyond the *A* cutoff point are all true positives (*TP*). Schematic **B** shows a test with 100% sensitivity (100% PV–) when the upper cutoff point is at *A*. Note that as sensitivity increases, the specificity and PV+ decrease because of an increase in false positives (*FP*). Schematic **C** shows a test with 100% specificity (100% PV+) when the upper cutoff point is at *B*. Note that as specificity increases, the sensitivity and PV– decrease because of an increase in false negatives (*FN*). *PV–*, Predictive value of a negative test result; *PV+*, predictive value of a positive test result. *(From Goljan E, Sloka K: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 5, Fig. 1-3.)*

Fetal RBCs containing HbF are destroyed by splenic macrophages. The unconjugated bilirubin derived from the initial destruction of fetal RBCs is responsible for physiologic jaundice of the newborn, which occurs ~3 days after birth.

4. HbF–containing cells are replaced by RBCs containing HbA (>97%), HbA_2 (2.0%), and HbF (1%).
5. Immunoglobulin (Ig) synthesis
   a. Synthesis of IgM begins shortly *after* birth.
   b. Newborns *lack* IgM isohemagglutinins (natural antibodies against blood groups) in their plasma.
      - For example, blood group A newborns lack anti-B IgM isohemagglutinin in their plasma.

Newborns: ↑HbF → left shift OBC → ↑EPO → ↑Hb, Hct, and RBC production

Clinical correlation: Newborns with an increase in cord blood IgM may have an underlying congenital infection (e.g., cytomegalovirus, rubella). Their blood should be screened for antibodies against the common congenital infections.

Newborns: lack IgM at birth; ↑cord blood IgM indicates congenital infection

6. IgG antibodies in newborns are of *maternal* origin.
   a. Newborns begin synthesizing IgG 2-3 months *after* birth.
   b. Adult levels of IgG are achieved by age 6 to 10 years.

Clinical correlation: A mother with a positive test for human immunodeficiency virus (e.g., IgG antibodies against the glycoprotein gp120) transplacentally transfers IgG antibodies to the fetus. This does *not* mean that the child is infected by the virus.

Newborns normally synthesize both IgM and IgG after birth

C. Children

1. When compared to an adult, children have *higher* serum alkaline phosphatase (ALP) levels.
   a. This is due to *increased* bone growth in children and release of ALP from osteoblasts.
   b. ALP removes the phosphate from pyrophosphate, which normally inhibits bone mineralization.
2. When compared to an adult, children have *higher* serum phosphorus levels.
   - For normal mineralization of bone to occur, phosphorus is required to drive calcium into bone; hence, the higher phosphorus levels in children.
3. When compared to an adult, children have a *lower* Hb concentration (11.5 g/dL; anemia <11.5 g/dL).
   a. This is most likely related to the increased serum phosphorus levels in children.
      - A proportionately greater amount of 2,3-bisphosphoglycerate (2,3-BPG) is synthesized because of the availability of phosphorus.
   b. Increasing 2,3-BPG synthesis causes a greater release of O_2 to tissue (right shifts the O_2 binding curve); hence, an 11.5 g/dL Hb concentration in a child delivers as much O_2 to tissue as a 13.5 g/dL Hb concentration does in an adult.

Children: ↑serum ALP, phosphorus, 2,3-BPG; ↓Hb

D. Adults

1. When compared to men, women have slightly *lower* serum iron, ferritin, and Hb levels (12.5 g/dL; anemia <12.5 g/dL), which is attributed to:
   a. Monthly menstrual flow
   b. Lower testosterone levels than men
      - Testosterone stimulates erythropoiesis, which also contributes to the higher Hb level in men (13.5 g/dL; anemia <13.5 g/dL) than in women.

Women: ↓Hb, iron, ferritin than men

2. Advanced age
   a. *Decrease* in the glomerular filtration rate (GFR) and creatinine clearance (CCr)
      - Potentially harmful to the proximal kidney tubules if nephrotoxic drugs (e.g., aminoglycosides) are *not* dose-adjusted to the age and GFR of the patient.

Elderly: ↓GFR, CCr; danger of drug toxicity in the kidneys

   b. *Increase* in serum ALP
      (1) Increase in serum ALP is of bone origin and relates to degeneration of articular cartilage in the weight-bearing joints (osteoarthritis), a condition that invariably occurs in the elderly.
      (2) Reactive bone formation (called osteophytes) occurs at the margins of the joints, leading to the slight increase in serum ALP.
   c. When compared to young adult males, there is a slight *decrease* in the Hb concentration in elderly males.
      (1) Hb drops into the range of a normal adult woman (12.5 g/dL; anemia <12.5 g/dL) and should *not* be misinterpreted as anemia.

Elderly: Hb decreases with age

      (2) Decrease in Hb parallels the normal decrease in testosterone associated with aging.
   d. Often a *loss* of blood group isohemagglutinins (e.g., anti-B IgM in a group A individual) occurs because of a *decrease* in antibody synthesis.

Clinical correlation: Loss of isohemagglutinins explains why some elderly individuals transfused with the wrong type of blood do *not* develop a hemolytic transfusion reaction. For example, a blood group A individual inadvertently transfused with group B blood may not hemolyze the group B RBCs, because they do not have anti-B IgM antibodies. This is *not* to say that elderly people can safely be given any blood group for transfusion; they should receive blood group and Rh type specific blood.

   e. *Decrease* in cell-mediated immunity
      - For example, a purified protein derivative test for tuberculosis is weakly reactive in elderly patients who have previously been exposed to tuberculosis.

Elderly: decrease in antibody synthesis and cellular immunity

E. Pregnancy

1. Normal *decrease* in Hb concentration
   a. Due to an *increase* in plasma volume (PV) and RBC production (RBC mass) with a much greater *increase* in PV than in RBC mass
      - *Dilutional* effect decreases the Hb concentration (normal 11 g/dL; anemia <11 g/dL).

Pregnancy: ↑↑plasma volume, ↑RBC mass; ↑GFR, CCr

   b. Other effects of an *increase* in PV include:
      (1) *Increased* GFR and CCr
      (2) *Increased* renal clearance of blood urea nitrogen, creatinine, and uric acid with corresponding lower levels in serum
2. *Increase* in serum ALP (placental origin)

Pregnancy: ↑serum ALP (placental origin)

3. *Increase* in serum human placental lactogen (HPL)
   a. Normally synthesized by syncytiotrophoblasts lining the chorionic villi in the placenta
   b. Inhibits the sensitivity of peripheral tissue to insulin
      - Produces the normal *glucose intolerance* in pregnancy
   c. *Increases* β-oxidation of fatty acids
      - Excess acetyl CoA is produced, leading to increased liver synthesis of ketone bodies and the normal *ketonemia* in pregnancy.

Pregnancy: ↑HPL causes ↓insulin sensitivity → mild glucose intolerance

4. Mild respiratory alkalosis
   a. Due to stimulation of the respiratory center by estrogen and progesterone
   b. Increased pulmonary clearance of CO_2 is responsible for the respiratory alkalosis and is not accompanied by an increase in respiratory rate.
   c. Decreased P_{CO_2} causes a corresponding *increase* in P_{O_2} in maternal blood, which increases the amount of oxygen that is available to the developing fetus.
      - Arterial P_{O_2} is usually >100 mm Hg in pregnancy.

Pregnancy: respiratory alkalosis due to estrogen/progesterone

5. *Increase* in the total serum thyroxine (T_4) and cortisol (refer to Chapter 23)
   a. Normal measurement of total serum T_4 and cortisol includes bound and free fractions.
   b. Estrogen increases liver synthesis of the binding proteins for T_4 (thyroid binding globulin) and cortisol (transcortin); however, the free hormone levels (metabolically active) are unaffected.
      - Because the free hormone levels are normal, the serum thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) are also normal.

Pregnancy: ↑total serum T_4/cortisol; free hormone levels are normal

F. Hemolyzed blood specimen related to venipuncture

1. Potassium is the major intracellular cation; therefore a hemolyzed blood sample *falsely increases* serum potassium (FP).
2. RBCs primarily use anaerobic glycolysis as a source of ATP; therefore lactate dehydrogenase (LDH), which normally converts pyruvate to lactate, is also *falsely increased* (FP).

Hemolyzed specimen: ↑serum K^+, LDH

CHAPTER 2 Cell Injury

I. Tissue Hypoxia

A. Hypoxia

Hypoxia: inadequate oxygenation of tissue

1. Definition—inadequate oxygenation of tissue
2. Factors contributing to the total amount of O_2 carried in blood
   a. Normally, O_2 diffuses down a gradient from the atmosphere to the alveoli, to plasma, and into the red blood cells (RBCs), where it attaches to heme groups (Table 2-1).
      (1) In the alveoli, O_2 increases the partial pressure of O_2 (PAO_2).
      (2) In the plasma of the pulmonary capillaries, O_2 increases the partial pressure of O_2 (Pao_2).
      (3) In the RBC, O_2 attaches to heme groups and increases the O_2 saturation (Sao_2).

O_2 diffusion: O_2 in atmosphere → ↑PAO_2 → ↑Pao_2 → ↑Sao_2

   b. Pao_2 and Sao_2 are reported in arterial blood gas analyses.
   c. O_2 content is a measure of the total amount of O_2 carried in blood and includes the hemoglobin (Hb) concentration as well as the Pao_2 and Sao_2.
      • Decrease in O_2 content due to a decrease in Hb, Pao_2, or Sao_2 causes an increase in erythropoietin (EPO; refer to Chapter 12).

O_2 content = (Hb g/dL × 1.34) × Sao_2 + Pao_2 × 0.003

3. In hypoxia, there is decreased synthesis of adenosine triphosphate (ATP).
   a. ATP synthesis occurs in the inner mitochondrial membrane by the process of oxidative phosphorylation (see later).
   b. O_2 is an electron acceptor located at the end of the electron transport chain (ETC) in complex IV of the oxidative pathway.
   c. Lack of O_2 and/or a defect in oxidative phosphorylation culminates in a decrease in ATP synthesis.

Hypoxia: ↓ATP synthesis by oxidation phosphorylation

Pulse oximetry (Fig. 2-1) is a noninvasive test for measuring Sao_2. It utilizes a probe that is usually clipped over a patient's finger. A pulse oximeter emits light at specified wavelengths that identify oxyhemoglobin and deoxyhemoglobin, respectively. The wavelengths emitted by a pulse oximeter *cannot* identify dyshemoglobins such as methemoglobin (metHb) and carboxyhemoglobin (i.e., carbon monoxide bound to Hb [COHb]), which normally decrease the Sao_2 (see later). In the presence of these dyshemoglobins, the oximeter calculates a falsely high Sao_2. Unlike the standard oximeter, a co-oximeter emits multiple wavelengths and identifies metHb and COHb as well as oxyhemoglobin and deoxyhemoglobin. Hence, in the presence of these dyshemoglobins, the Sao_2 will be decreased. Pulse oximeters are very useful in following patients with respiratory failure, severe bronchial asthma, obstructive sleep apnea, and those under general anesthesia.

Pulse oximeter: falsely ↑Sao_2 in metHb and COHb

Co-oximeter: accurately measures ↓Sao_2 in metHb, COHb

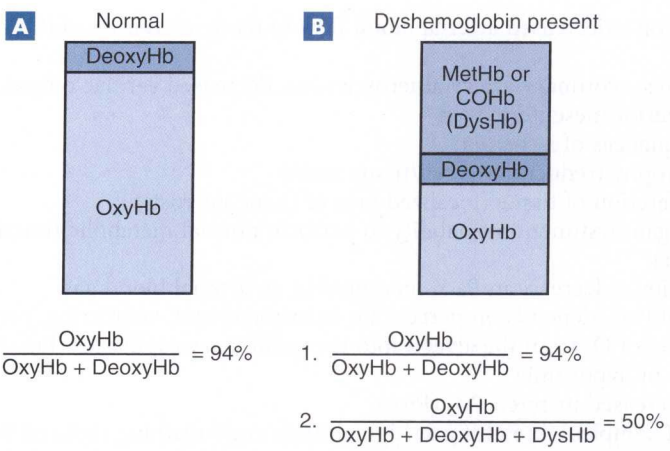
4. Clinical findings in hypoxia
   a. Cyanosis (bluish discoloration of skin and mucous membranes) (Fig. 2-2)
   b. Confusion
   c. Cognitive impairment
   d. Lethargy

Cyanosis: clinical finding in hypoxia

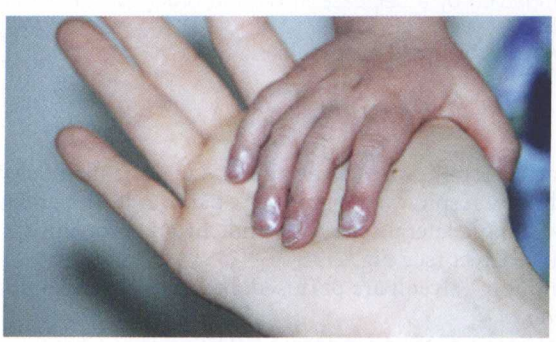
TABLE 2-1 Terminology Associated with Oxygen Transport and Hypoxia

TERM	DEFINITION	CONTRIBUTING FACTORS	SIGNIFICANCE
O_2 content	Total amount of O_2 carried in blood O_2 content = (Hb g/dL × 1.34) × SaO_2 + PaO_2 × 0.003 ↑O_2 content causes ↓EPO ↓O_2 content causes ↑EPO	Hb concentration in RBCs (most important factor) PaO_2 SaO_2	Hb is the most important carrier of O_2 Hb concentration determines the total amount of O_2 delivered to tissue
PaO_2	Pressure keeping O_2 dissolved in the plasma of arterial blood (PaO_2 x 0.003)	Percentage of O_2 in inspired air Atmospheric pressure PAO_2 concentration in the lungs Normal O_2 exchange in the lungs thru the alveolar-capillary membrane	Reduced in hypoxemia Driving force for diffusion of O_2 from the capillaries (higher concentration of O_2) into tissue (lower concentration of O_2)
SaO_2	Average percentage of O_2 bound to Hb in the RBCs	Same factors listed above for PaO_2 Valence of heme iron in each of the four heme groups in RBCs Fe^{2+} (reduced, ferrous) binds to O_2 Fe^{3+} (oxidized, ferric) does *not* bind to O_2	SaO_2 <80% produces cyanosis of skin and mucous membranes

EPO, Erythropoietin; *Fe^{2+}*, ferrous iron; *Fe^{3+}*, ferric iron; *Hb*, hemoglobin; *O_2*, oxygen; *PAO_2*, partial pressure of alveolar Po_2; *PaO_2*, partial pressure of arterial oxygen; *SaO_2*, arterial oxygen saturation.



2-1: Pulse oximetry is a noninvasive alternative for measuring SaO_2. It utilizes a probe that is usually clipped over a patient's finger. The oximeter emits red and infrared light at specified wavelengths that identify oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb), respectively. The oximeter calculates the SaO_2 using the following equation: oxyHb/oxyHb + deoxyHb (**A**). The wavelengths emitted by a pulse oximeter *cannot* identify dyshemoglobins such as metHb and carboxyhemoglobin (i.e., carbon monoxide bound to Hb, [COHb]), which normally decrease the SaO_2. In the presence of these dyshemoglobins, the oximeter calculates a normal SaO_2, because metHb or COHb are *not* included in the calculation of SaO_2 in the equation in *1* (**B**). However, a co-oximeter, which emits multiple wavelengths, calculates the decrease in SaO_2, because it identifies metHb and COHb and includes them in the calculation of SaO_2: oxyHb/oxyHb + deoxyHb + MetHb or COHb (equation *2* in **B**). *(From Goljan E, Sloka K: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 78, Fig. 3-6.)*



2-2: Hand of a child with tetralogy of Fallot, a congenital heart disease associated with cyanosis. Note the blue-discoloration beneath the nails and the duskiness of the skin when compared to the hand of a normal adult. *(From Taylor S, Raffles A: Diagnosis in Color Pediatrics. London, Mosby-Wolfe, 1997, p 91, Fig. 3.6)*

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