CLINICAL INTERPRETATION OF LABORATORY TESTS

FRANCES K. WOMACK

CHEMISTRY 4

URIC ACID (250-750 mg. / 24 hrs.)

BLOOD AMMONIA

PREGNANCY TEST

OTHER

CHEMISTRY 5

REPORT DATE

CYTOPATHOLOGY

MISC. LAB. 1

REPORT DATE

B.S.P.
PATIENTS WT. ____ LBS. 0

CREATININE CLEARANCE
HT. ____ FT. ____ IN. WT. ____ LBS. 70-130

STOOL FOR OCCULT BLOOD NEG

OTHERS (Specify)

MISC. LAB. 2

REPORT DATE

GASTRIC ANALYSIS

REPORT DATE

AMOUNT C.C.
FOOD C.C.
COLOR
MUCUS
BILE
BLOOD
FREE ACID
TOTAL ACID
ORG. AC.
OCC. BLOOD
TIME
MICROSCOPY

GENTAMYCIN
KANAMYCIN

Report Date

BACTERIOLOGY

CHEMISTRY 4

URIC ACID (250-750 mg. / 24 hrs.)

OTHER

CHEMISTRY 5

REPORT DATE

CYTOPATHOLOGY

REPORT DATE

LBS. 0

70-130

NEGA

MISC. LAB. 2

REPORT DATE

BACTERIOLOGY

CLINICAL INTERPRETATION OF LABORATORY TESTS

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PREFACE

The range of laboratory tests continues to expand. More tests are done; more money is spent; more data are generated than ever before. How can the individual clinician, caring for individual patients, hope to make optimal use of the laboratory and assimilate the information thus generated? In an era of intense specialization and maxi-experts who limit themselves to mini-subjects, the patient is the ultimate generalist. His complaints and concerns cover all areas. The clinician caring for the patient must be conversant with the diagnostic procedures that he, or others, employs to illuminate these concerns.

This book comes from the pen of an individual, rather than the pens of a group, but draws upon the work of many persons in the field. My aim is to assist primary care providers to select laboratory procedures and evaluate results as they apply to the many possible problems that individual patients embody. The emphasis is on pathophysiology of disease states, not the technical details of laboratory procedures. In this way, I hope to provide both clinician and laboratory worker with a conceptual framework that puts disease and diagnosis into perspective. The laboratory worker and the clinician approach the patient from very different starting points, but both have the same goal in mind: optimal patient care.

This eighth edition of *Clinical Interpretation of Laboratory Tests* has a format different from that of its predecessors. Rather than divide the book into two divisions, Laboratory Principles and Clinical Findings, I have organized the chapters into the sectional categories that most laboratories employ: Hematology, Immunology, Chemistry, Microbiology, etc. All of the material on hematology, immunology, blood banking, and coagulation is new for this edition, as are the chapters on liver function tests and pregnancy. More than half of the previous edition has thus been completely replaced. In other chapters, new sections extensively replace or augment material from the seventh edition, especially in considering blood lipids, serum

isoenzymes, anaerobic microbiology, mechanisms of antibiotic activity, and Legionnaires' disease.

As always, I owe much to colleagues and students, especially the students in Duke University's Medical Technology, Pathologist's Assistant, and Physician's Associate programs. Their lively interest and intellectual curiosity remind me continually that all our facts, theories, and answers are only the foundation for further questions. The drawings are from the very helpful and cooperative pen of Mr. Donald Powell. I am particularly indebted to Linda Brogan, who did most of the typing, along with Diane Evans and Marjorie Penny. Their cheerful assistance was invaluable.

A book like this is never finished. Even as it goes to press, there are exciting new items I would like to work in. Judith Kim and Nancy Schmidt of the F. A. Davis Company did everything possible to help me with this eighth edition, and I thank them for their efforts.

Frances K. Widmann, M.D.

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SECTION 1

HEMATOLOGY

CHAPTER 1

HEMATOLOGIC METHODS

Blood constitutes 6 to 7 percent of total body weight—nearer to 7 percent in men and 6 percent in women. Plasma, the fluid portion of blood, comprises 45 to 60 percent of this total, while red blood cells occupy most of the remaining volume. White blood cells and platelets, although functionally essential, occupy a relatively small proportion of total blood mass. Hematology traditionally limits itself to the cellular elements of blood and the physiologic derangements that affect their functions. Hematologists also study blood volume, the flow properties of blood, and the physical relationships between red cells and plasma. The innumerable substances dissolved or suspended in the plasma fall into other laboratory disciplines.

The principal function of circulating blood is transportation; temperature regulation and the regulation of fluid and acid-base equilibrium are functions somewhat distinct from the purely transportive role. Red blood cells remain within the blood throughout their normal lifetime; they effectively transport oxygen without leaving the cardiovascular tree. White cells, on the other hand, perform their physiologic roles within tissue; while in the blood, they are merely in transit. Platelets exert their effects at the wall of blood vessels; circulating platelets do not, as far as we know, perform any specific function in the blood stream itself.

HEMATOPOIESIS AND BONE MARROW EXAMINATION

Except for some lymphocytes, blood cells in normal adults are manufactured in the marrow of a relatively few bones, notably the sternum, ribs, vertebral bodies, pelvic bones, and the proximal portions

of humerus and femur. In the fetus, mesodermal derivatives in other locations actively produce blood cells. The liver, the spleen, and the marrow cavities of nearly all bones are active hematopoietic sites in the newborn. Adult reticuloendothelial tissues retain the potential for hematopoiesis, although in a healthy state, reserve sites are not activated. Under conditions of hematopoietic stress in later life, liver, spleen, and an expanded bone marrow may resume producing blood cells.

Evaluating Hematopoiesis

Hematopoietic activity can be evaluated by examining bone marrow tissue, by measuring systemic uptake and incorporation of known precursor materials, and by using x-ray or radioisotope techniques to identify and characterize sites of hematopoietic activity. Microscopic examination of aspirated marrow is usually the first step, and the results determine whether other procedures are indicated. Obtaining bone marrow requires introducing a needle through the outer bony layers into the semisolid marrow and withdrawing a sample for examination.

ASPIRATION AND BIOPSY

In the adult, marrow is most accessible in the sternum and the anterior and posterior iliac crests. In very young children, the proximal portion of the tibia gives good results, while in older children, the vertebral bodies often are used. Hematopoietic bone marrow contains fat and other connective tissue as well as blood-forming cells. It is fluid enough to be aspirated through a needle, but only the first few drops should be used for examination because, in the later aliquots, fluid blood dilutes the marrow material. Tiny fragments of connective tissue as well as free-floating cells will be withdrawn. The morphology of these free cells provides much useful information but does not indicate the in situ relationship of hematopoietic cells to bone, fat, connective tissue, or other elements.

Sometimes marrow cellularity and tissue relationships can be estimated from paraffin sections of the clotted, aspirated material, but often a larger sample of intact tissue is needed. Specially designed biopsy needles make it possible to remove a cylinder of intact marrow tissue and overlying bone. This usually is done from the iliac crests, but if some other site is known or suspected to be abnormal, that site can be sampled. Occasionally, open surgical biopsy is necessary.

Meticulous aseptic technique is necessary, since infectious material introduced into bone marrow rapidly reaches the entire circulation. Skin and subcutaneous tissues usually are anaesthetized by local injection, but the patient often experiences some discomfort when the needle penetrates the periosteum; many patients perceive a "pulling" sensation at the moment of aspiration. Once the needle is withdrawn, firm pressure is needed to prevent hemorrhagic complications. Applying pressure is easiest over the sternum and most difficult over the iliac crests, especially in an obese individual.

M:E RATIO

Cells normally present in hematopoietic marrow include granulocytes and erythrocytes in all stages of maturation; megakaryocytes, the large, multinucleated cells from whose cytoplasm platelets develop; moderate numbers of lymphocytes; and occasional plasma cells. Although circulating blood contains 1000 times as many red cells as white cells (5 million red cells/mm.^{3}, as compared with 5,000 to 10,000 white cells/mm.^{3}), nucleated white cells in the bone marrow outnumber nucleated erythrocytic cells by about 3 to 1. This is called the *M:E* (myeloid to erythroid) *ratio*. Many factors contribute to this disproportion.

Red cells require 5 to 6 days for bone marrow development, but the nucleus disappears after 2 to 3 days.[5] Maturing red cells enter the circulating blood very promptly, even before the last maturational events have occurred. Red cells remain in the circulation for about 120 days before senescence and destruction. Nucleated granulocytic cells are numerous in the marrow because granulocytes have conspicuous nuclei throughout the 5 to 7 days of marrow development and large numbers of mature cells remain within the marrow as a "storage pool." On an average, granulocytes spend only 1 day in the circulating blood and have a total life span of only 9 to 15 days. The combination of massive granulocyte turnover, persistence of the nucleus, and marrow retention of mature cells makes the myeloid series the predominant nucleated form when marrow is examined. The normal M:E ratio is between 2:1 and 4:1.[40,50]

MARROW DIFFERENTIAL

Different sources give somewhat different values for normal proportions of marrow cells. The reasons for this variation are numerous.

Criteria for classifying cells differ; data about truly normal bone marrows are relatively sparse; the range of variation among normals is wide; and techniques for examination are various. Terminology for granulocyte maturation is fairly standard, but erythroid cells are described in several different terminologies (see Table 1). Table 2 indicates the range of "normal values" for cells in aspirated marrow. Paraffin-embedded tissue sections are unsuitable for detailed morphologic differentiation, but the approximate M:E ratio, the number of megakaryocytes, and the existence of severe cellular disproportions can easily be observed.

Sometimes aspirated material does not contain hematopoietic cells. This condition, called a "dry tap," occurs when hematopoietic activity is so sparse that virtually no cells exist to be withdrawn or when the marrow contains so many tightly packed, sticky, highly immature cells that gentle suction cannot dislodge them. If aspiration is unsuccessful, needle biopsy or open biopsy readily reveals what is wrong with the marrow.

INDICATIONS

Bone marrow examination is virtually diagnostic in multiple myeloma and in most leukemias, both acute and chronic. Lymphomas are best diagnosed by lymph node examination, but, after the diagnosis has been made, it often is desirable to determine whether there is lymphoma in the bone marrow. Bone marrow frequently is examined to search for metastatic spread of carcinoma; dissemination of systemic infections, especially tuberculosis; or the existence of generalized diseases that affect macrophages, such as lipid or glycogen storage diseases. Evaluating the marrow for evidence of increased or decreased cellular proliferation helps to determine whether deficient production or increased destruction is causing a patient's anemia or cytopenia, although this may not reveal the reason for the difficulty. In conditions of megaloblastic erythroid maturation or disordered iron metabolism, the bone marrow morphology may be highly revealing.

If the bone marrow shows little erythropoietic activity, the patient is said to have *hypoplastic anemia*. This is a description, not a diagnosis, and the cause for depressed erythropoiesis still must be sought. Common causes include chronic infection, hypothyroidism, chronic renal failure, advanced liver disease, and a range of "idiopathic" conditions. If an anemic patient has *erythropoietic hyperplasia*, many conditions must be considered. Marrow hyperactivity is characteristic

Table 1. Maturation of Erythrocytes

	Nucleus	*Cytoplasm*	*Size (μm.)*
Pronormoblast (Rubriblast)	Dispersed or granular chromatin Nucleoli present	Scant, medium blue No hemoglobin	18–25
Basophilic normoblast (Prorubricyte, early erythroblast)	Chromatin clumped in spoke-like pattern No nucleoli	Deep blue Polyribosomes numerous No hemoglobin	14–18
Polychromatophilic normoblast (Rubricyte, late erythroblast)	Chromatin in irregular lumps Occupies less than one-half of cell	Grayish-purple or greenish-purple Modest number of ribosomes, some unaggregated Hemoglobin present	12–15
Orthochromic normoblast (metarubricyte, normoblast)	Densely pyknotic Occupies one-fourth or less of cell	Grayish-pink Few polyribosomes, some unaggregated ribosomes Substantial hemoglobin	9–13
Reticulocyte	No nucleus	Uniformly pink, faintly gray Scattered residual RNA structures	9–10
Mature erythrocyte	No nucleus	Pink with central pallor No RNA	6–8

of iron deficiency anemia; thalassemias; hemoglobinopathies; pernicious anemia and other diseases of folate and B_{12} metabolism; hypersplenism; enzyme deficiencies such as G-6-PD deficiency, hereditary spherocytosis, and other membrane abnormalities; and destructive processes like antibody-mediated, bacterial, or chemical hemolysis. In pernicious anemia and other disorders of vitamin B_{12} or folic acid metabolism, developing red cells have a peculiar appearance called *megaloblastic maturation*. Except for this readily detected morphologic abnormality, the appearance of the hyperplastic marrow usually gives few clues to the specific diagnosis.

Table 2. Differential Counts of Nucleated Bone Marrow Cells*

	Range of Mean Values†	*Range of Ranges Given*
Myeloblast	0.3–2	0–5
Promyelocyte	1.4–5	0–8
Myelocyte	4.2–8.9	0–15
Metamyelocyte	6.5–22	3–32
Band	13–24	12–34
Mature granulocyte		
Neutrophil	15–20	5–32
Eosinophil	0.5–2	0–6
Basophil	0–0.2	0–5
Lymphocyte	14–16	3–26
Monocyte	0.3–2.4	0–6
Plasma cell	0.3–1.3	0–3.9
Pronormoblast	0.2–0.6	0–1.3
Basophilic normoblast	1.4–2	0–4
Polychromatophilic normoblast	6–21	4–29
Orthochromic normoblast	1–3	0–4.6
M/E ratio	2.3–3.5 to 1	1.5–8 to 1

*Figures are for adults and are taken from several series as reported in Williams[54] and Wintrobe.[55]
†Values are expressed as percent of nucleated cells present.

Regulation of Marrow Activity

ERYTHROPOIETIN

Red-cell production is largely regulated by *erythropoietin*, a heat-stable α-globulin produced by the kidney. Reduced tissue oxygen levels stimulate secretion of erythropoietin. It is unclear where and how tissue hypoxia conveys the need for erythropoietin to the kidney; such communication may occur within the kidney itself.[5] Very slight changes in oxygenation have this effect. Tissue oxygen levels may change as a result of altered blood hemoglobin concentration, altered oxygen affinity of hemoglobin, reduction in hemoglobin oxygen saturation, or changes in pattern or spread of blood flow. When hemoglobin and tissue oxygenation are normal, small amounts of erythropoietin are excreted in urine. Anemic or hypoxic patients usually have much increased urinary erythropoietin levels.