HANDBOOK OF CLINICAL PATHOLOGY

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Preface

This *Handbook of Clinical Pathology* is designed to provide an up-to-date, concise guide for medical students and practicing physicians through the *maze* of clinical pathology, providing the "why" of clinical laboratory procedures as well as the significance and limitations of these laboratory tests. Essentially, this text provides the facts needed for intelligent ordering of laboratory tests and interpretation of the results of laboratory tests.

For paramedical personnel such as nurses, radiology technicians, medical assistants, medical technologists, and laboratory technicians, this text is designed to bridge the gap between the voluminous, detailed "how-to" textbooks of clinical pathology and the superficial survey books on clinical pathology.

The text is designed to provide a physiological and biochemical basis for the laboratory tests described, so that each test can be intelligently evaluated. Except for some tests that are frequently performed by physicians (such as bleeding time), this text assiduously avoids the detailed "how-to" approach to tests. Enough background in methodology is given, however, to enable the physician to evaluate the methods used in the laboratories that analyze the specimens from his patients.

When the diagnosis of a disease or disease group such as the lymphomas is based primarily on anatomic findings, the reader is referred to appropriate reference in the companion texts, *The Bare Facts of General Pathology* (ed. 2, 1974) and *The Bare Facts of Systemic Pathology* (1972), published by the J. B. Lippincott Company.

This text is organized as much as possible with a systemic approach because when most doctors are interested in enzymes or other laboratory tests, they want to know the relationship of a test or group of tests to a disease—such as myocardial infarction—and are not interested in a study of "enzymes for enzymes' sake," as in the usual biochemical textbook

fashion. There are some areas, however, that have been handled in the traditional clinical pathology (procedural) text approach because they cross many systemic areas. Examples of these are serology, microbiology, and blood banking.

The use of this text should help medical students, physicians, and paramedical personnel better understand the intelligent use of the laboratory in the care of patients.

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JOSEPH A. SISSON, M.D.

Contents

1

Introduction to Laboratory Tests and Concepts

What is Clinical Pathology? Clinical pathology, also often called "laboratory medicine," is that branch of pathology which is concerned with the examination of all specimens removed from patients by the following methods:

1. Chemical
2. Microbiologic parasites and other organisms
3. Serologic
4. Hematologic
5. Immunohematologic
6. Isotopic, including radioimmunoassay

In some hospitals the pulmonary function, BMR and EKG labs are also run by clinical pathologists, and in some they are separate laboratories.

Not ordinarily included in clinical pathology are the following:

1. Surgical pathology
2. Autopsy pathology
3. Cytology
4. Forensic pathology

What tests are and are not done in the clinical pathology laboratory in any particular hospital is based more on local medical politics than on the methodological classification of the test in question.

Why do physicians order laboratory tests? The following twelve reasons are commonly listed as valid reasons for ordering laboratory tests:

1. To make a definitive diagnosis
2. To confirm a clinically suspected diagnosis
3. To rule in (or out) a differential diagnosis list
4. To screen for occult disease
5. To assist medicolegal purposes
6. To determine the severity of disease (usually an acute disease)
7. To determine the stage of disease (usually a chronic disease)
8. To assist in determining therapy or the effect of therapy
9. To assist in decisions concerning disposition of the patient
10. To prepare the patient for a routine admission or operation
11. To assist in genetic counseling
12. To allow time for further patient observation

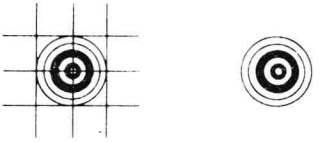

FIG. 1-1. Test specific and accurate for one parameter.

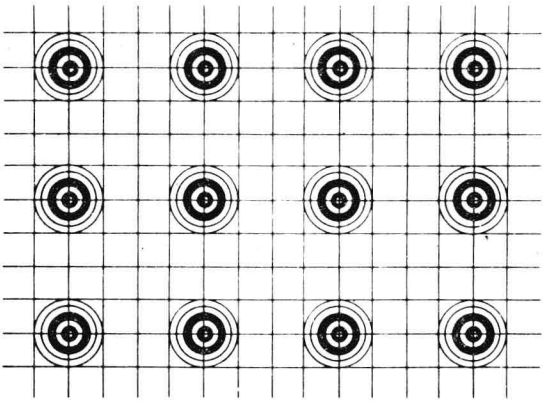

FIG. 1-2. Test sensitive for twelve parameters.

CHARACTERISTICS OF AN EFFECTIVE LABORATORY TEST

Theoretically, the ideal laboratory test would be accurate, precise, sensitive, specific, fast, and inexpensive and would always be able to differentiate normal or well patients from abnormal or sick patients. Of course, *NO* test or group of tests fulfills all of the above ideal criteria. However, equipped with certain knowledge about the characteristics, limitations, and costs of certain laboratory tests, the physician can use the laboratory effectively as an aid in making intelligent diagnoses.

Now we will explore some of the terms used above as they apply to clinical pathology.

1. *Precision:* Precision is defined as the ability to reach or hit a given value repeatedly. A precise test may *NOT* be an accurate test measuring the *true* value of a test. Figure 1 shows a precise test hitting the target on the left each time it is performed. The concept of precision relates more to the test method than to the level of a test substance in the patient's sample.

2. *Accuracy:* The accuracy of a test refers to its proximity to the *true* value of the level or number in the sample being tested. A certain amount of accuracy is desired; however, tests that are too accurate probably will be too expensive and time-consuming to be clinically useful.

3. *Sensitivity:* The sensitivity of a test is its ability to detect a given substance. Theoretically, a highly sensitive test is desirable; however, because nearly all normal tissues and fluids have *some* (often very small or low) level of nearly all biologic materials (e.g., enzymes, chemicals, cells), a test that can only detect *ABNORMAL* levels is often more desirable in clinical medicine than a supersensitive test. For example, the stool guaiac is more desirable for detection of occult blood in the stool than is the much more sensitive benzidine or the ultrasensitive orthotoluidine test. This is true because there are normally up to 3.0 cc of occult blood in the stool per day due to rough material passing through the G.I. tract. The purpose of looking for occult blood in the stool is to find *significant* occult blood *above* the normal levels. For this purpose, the

guaiac is superior to the 10 to 1000 times more sensitive benzidine and orthotoluidine tests.

4. *Specificity:* The specificity of a test refers to its ability to detect a given substance to the exclusion of all other substances. Theoretically, a specific test would have 100% ability to pick up a given substance with no false positives or false negatives. Figure 1 indicates that a specific test would always pick up the target on the left, never the target on the right. Figure 2 would characterize a very nonspecific but very sensitive test or group of tests able to pick up twelve different substances but not able to differentiate between them. Examples of such a test are the CRP and sed rate, which are abnormal in many diseases but which do not differentiate between disease entities.

In general,

1. Tests that are highly sensitive are not highly specific and vice versa.
2. Tests with high specificity tend to be time-consuming and expensive.
3. For screening procedures, sensitive, less expensive tests are used.
4. For definitive diagnostic purposes, more expensive specific tests are often justified.

ECONOMICS OF LABORATORY TESTING

Appropriate use of laboratory tests can save money by facilitating a rapid and accurate diagnosis. Thus proper therapy can be started soon, saving hospital days and days out of work for the patient.

The indiscriminate use of laboratory tests or their improper interpretation can add unnecessarily to the patient's hospitalization costs indirectly through prolonged hospital stays and directly through added laboratory and other procedural costs. There is NO absolute guide for ordering laboratory tests. The best overall guide for the physician is to question: Is this test really necessary? Will it yield clinically useful information? If the test is a very expensive procedure (e.g., TSH, LATS), have all of the other less expensive tests in the area failed to yield the correct diagnosis? If the answer to one or more of these questions is yes, then the test in question is probably justified.

CONCEPT OF NORMAL

In laboratory testing, as in all other parameters evaluating large populations, there is a gaussian distribution of all subjects around an average or mean value. In laboratory testing, the following limits are arbitrarily set as NORMAL.

Normal = average plus or minus two standard deviations (± 2SD) with 95% confidence level. This means that 5%, or 1 in 20, normal (healthy) people will have a value outside the ± 2SD limit. This is an arbitrary concept; but if the limit were set at ± 1SD with 67% confidence level, ⅓ of the normal population would be outside the normal range. If the limit were set at ± 3SD with 99% confidence limit, only 1% of the normal population would be outside the normal range. Because of the overlap of the normal and abnormal curve, many abnormal (sick) people would have normal values. The curves below show some of the problems in setting normal and abnormal values for any given test.

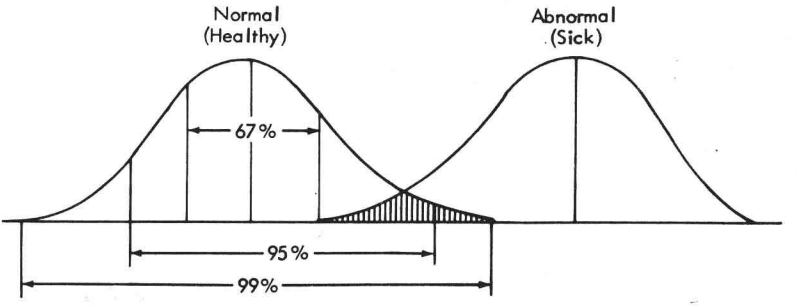

FIG. 1-3. Distribution of healthy and sick populations showing overlaps.

Abnormal. From the above bellshaped curves, it can be seen that the abnormal or sick patients with an abnormal laboratory test are also distributed in a gaussian manner similar to the healthy population. The hardest problem is to distinguish the sick from the healthy population when the values fall in the overlap (hatched) area on the above graph. There is no absolute method to distinguish healthy from sick based on any test in existence, especially when the results are in the overlap area; however, some guides are as follows:

1. The further from ± 2SD the abnormal result is, the more likely it is to be significant.

Borderline value = values greater than ± 2SD but under ± 3SD from the normal mean value

Biologically significant value = values over ± 3SD from the normal mean

2. This statistical concept is not a great impedance to medical diagnosis because the physician uses a multitude of data in making a clinical diagnosis, not just *ONE* laboratory test. He uses the history, physical findings, several laboratory findings, x rays, EKG's, EEG's, and other special procedures to make a diagnosis.

QUALITY CONTROL IN THE LABORATORY

All laboratories, especially those in hospitals and those engaged in interstate commerce, must have an extensive, approved quality control (QC) program. QC consists of running a number of assayed and unassayed samples for the parameter being tested in order to assure that the laboratory techniques are capable of the precision, accuracy, sensitivity, and specificity necessary to produce reliable, clinically useful results.

There are no absolute limits for precision or accuracy. These QC results are recorded, and the mean and SD for the test in question are set up. Each time the procedure in question is performed the running of suitable QC specimens assures that all the ingredients in laboratory testing—e.g., the technician, the method, the instrument(s), the reagents, and the samples—are interacting within the prescribed limits.

When the physician questions a given laboratory's results, he should go to the laboratory and look at the QC for that procedure to learn the significance of the results reported in terms of QC for that laboratory.

There should always be open communication between the laboratory director or clinical pathologist and the practicing physicians in any hospital so that any problems in laboratory tests can be rapidly resolved; no book can possibly furnish the magic formula to solve all problems of laboratory testing.

COLLECTION OF LABORATORY SPECIMENS

Properly obtaining the specimen for laboratory examination is the most important thing that the physician or non-laboratory personnel can do to insure meaningful results. In general, the proper collection

of specimens, rapid delivery to the laboratory, and a properly completed requisition will produce the best possible and most meaningful results on all specimens. The following are a few guidelines for specimen collection:

I. Timing

A. *Laboratory schedule:* Specimens are usually best handled in laboratories on weekday mornings when the largest number of most experienced technicians and technologists are on duty. If specimens are to be sent to another city for analysis, they are best sent on Monday or Tuesday. Otherwise, they may end up sitting in a hot or a cold post office over the weekend with deterioration of the specimen.

B. *Patient's disease:* Specimens should be drawn when chances of obtaining diagnostic information are the greatest. Some examples are:

1. Malaria smears and blood cultures for SBE—during fever spike
2. Cardiac enzymes—3 × day, etc.
3. Diabetes—FBS, GTT
4. Pregnancy tests—morning urine

C. *Diet:* Many tests are interfered with by a non-fasting specimen; e.g. FBS with serum triglyceride, 5 HIAA with bananas, etc. The specimen must be collected in proper relation to dietary intake.

II. Proper Specimen in Proper Containers

A. CBC—must have non-hemolyzed, anticoagulated blood

B. Most lab tests on serum—freshly clotted, non-hemolyzed blood to draw serum from

C. Blood and other cultures—must be drawn under sterile conditions without contamination by other, saprophytic bacteria

D. Blood gases—heparinized anerobic, cold (not frozen) specimen

III. Inform the Patient

One of the biggest sources of medicolegal action by patients is in the area of the informed and implied consent. When

entering the hospital, the patient signs his consent to the performance of certain procedures ordered by his physician. However, recently numerous medicolegal actions have been won because the consent was not INFORMED. In other words, the patient was not *informed* about what was being done to him. When performing a procedure, the least one can do is say, "A blood test (or a 24 hr. urine) has been ordered by your physician. In order to obtain the best results we need you to hold your arm out (or save your urine in this jug) so that we can perform the test ordered by your physician."

Summary

The general considerations in the proper collection of clinical laboratory specimens are outlined above and in the various sections of this book. Since details of how different labs want specimens collected and specimens vary greatly, it is recommended that the person obtaining specimens follow the explicit directions outlined in the procedures manual published by the laboratory where the specimen in question is to be sent.

2

Multiphasic Screening and Use of Modern Laboratory

TERMS—DEFINITIONS AND CONCEPTS

TERMS	*DEFINITIONS AND RELATED CONCEPTS*
Screening Test	(A) Definition: a test or procedure designed to "rule in" or "rule out" the presence of a given disease entity in a patient; e.g., a high blood sugar is indicative of diabetes mellitus but also of many other states, such as the postprandial state, Cushing's syndrome, pheochromocytoma, and hyperthyroidism.
	(B) Criteria for the "ideal" screening test 1. Rapid results 2. High sensitivity. High specificity is also desirable but usually is sacrificed for high sensitivity, rapidity, and economy. 3. Low cost; e.g., VDRL—$3.00 screening test for syphilis, FTA—$18.00 diagnostic definitive test for syphilis 4. Limitations of screening tests—in general, screening tests cannot be used ALONE to make a definitive diagnosis.
Definitive Test (Diagnostic)	(A) Definition: a test or procedure, the results of which are DIAGNOSTIC for a given

Definitive Test (Diagnostic; Continued)

disease entity in a patient. Ideally, this should be a single test or procedure.

Examples:

1. Positive FTA test is diagnostic for syphilis.
2. An acidic pH below 7.3 is diagnostic of acidosis.

(B) Criteria for a "definitive test"

1. Highest specificity: A test that when positive is diagnostic for a given disease state without further procedures.
2. Cost: Because many definitive tests are very time consuming, cost is *not* a major consideration in their performances as in screening tests; e.g., if a $3.00 VDRL (screening) test is positive and a BFP is suspected, an $18.00 FTA (definitive) test is ordered to rule out syphilis.
3. Sensitivity: Because many definitive tests are *so* specific, they are of low sensitivity and therefore are often poor screening tests; e.g., the FANA test is positive in 99% of LE cases but also positive in many other diseases. The classic LE Prep is positive in 60–75% of LE cases and is very uncommonly positive in any other diseases.
4. Limitations: Frequently there is no *single* absolutely diagnostic or definitive test for a given disease or disease entity.

   USUALLY A GROUP OF TESTS AND CLINICAL EVALUATION OF THE PATIENTS ARE NECESSARY TO MAKE THE PROPER DIAGNOSIS.

   E.g., diabetes mellitus is usually defined by an abnormally shaped GTT after ingestion of a certain amount of glucose. However, the patient must have been