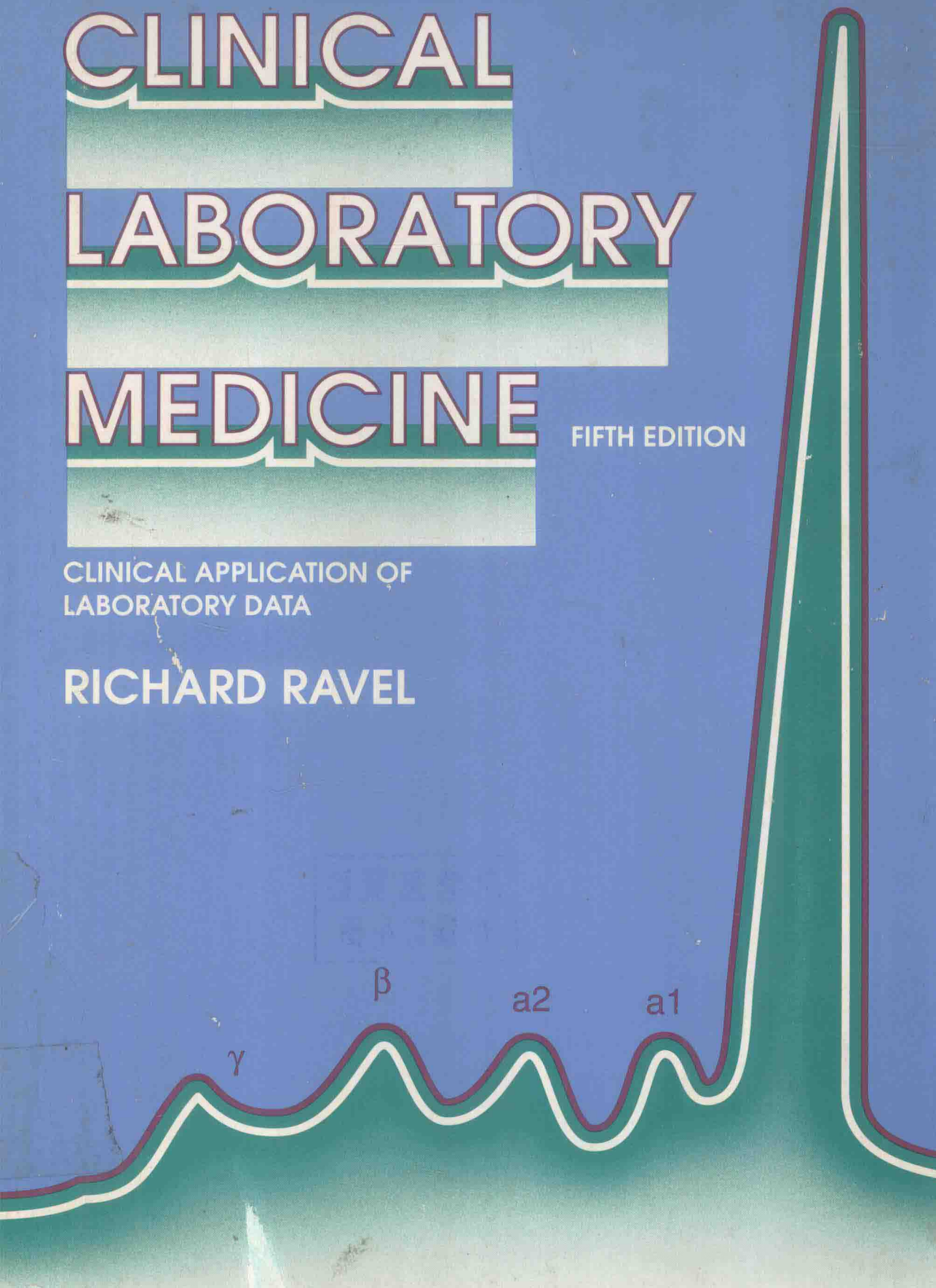
CLINICAL LABORATORY MEDICINE

FIFTH EDITION

CLINICAL APPLICATION OF LABORATORY DATA

RICHARD RAVEL



Clinical Laboratory Medicine: Clinical Application of Laboratory Data

Fifth Edition

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PREFACE TO THE FIRST EDITION

The clinical laboratory has a major role in modern medicine. A bewildering array of laboratory procedures is available, each of which has its special usefulness and its intrinsic problems, its advantages and its drawbacks. Advances in biochemistry and radioisotopes, to name only two conspicuous examples, are continually adding new tests or modifying older methods toward new usefulness. It seems strange, therefore, that medical education has too often failed to grant laboratory medicine the same prominence and concern that are allotted to other subjects. If ever a comprehensive, systematic and critical teaching system were needed, it is for this complex and heterogeneous topic. It would seem that if one were to consider ordering any laboratory procedure, several things should be known about the test, including:

1. In what situations is the test diagnostic, and in what situations does the test provide information without being diagnostic?

2. What commonly available tests give similar information, and when should one be used in preference to the others?

3. What are the disadvantages of the test and possibilities of error or false results?

The fact that this type of information is not adequately disseminated is quickly brought home to a clinical pathologist, who supervises the clinical laboratory and at the same time acts as liaison to clinicians on laboratory problems. It becomes quickly evident in two ways—the continually rising number of laboratory procedure requests and even a casual inspection of patients' hospital charts. Unnecessary tests represent severe financial and personal inconvenience to the patient; inappropriate tests or tests done under improper conditions mean wasted or misleading information, and often a loss of precious time.

In laboratory medicine, textbooks are available, as in all areas of general medicine considered detailed enough to warrant a specialty status. These fall into two groups: those mainly for the technician and those designed for clinicians. Technician-oriented books necessarily stress the technical aspects of individual tests, with emphasis on cookbook methodology. Textbooks for the clinician vary considerably in approach. Some excellent works concentrate almost exclusively on one subject or subspecialty, such as hematology. Many others combine technician methodology with discussion to varying degrees of the clinical aspects of tests. The latter aspect often suffers due to inevitable limitations imposed by mere length. Some texts which emphasize the clinical approach may be criticized on the grounds that they neglect either adequate attention to possible limitations and sources of error in each particular laboratory procedure, or fail to delineate the background or the technical aspects of the tests enough to provide a clear picture as to just what information the test actually can provide.

This volume attempts to meet these criticisms. Its aim is to provide enough technical and clinical information about each laboratory procedure included so as to allow adequate understanding, selection and interpretation of these procedures. Many of the laboratory tests require varying amounts of individual discussion. Others are noted in the context of the diseases in which they may be useful. In addition, most of the common diseases in which laboratory tests render significant assistance are briefly outlined, and the role of the laboratory in each is explained. Also included are a considerable number of diseases or conditions which are uncommon or even rare, but which may be considered important from various points of view—either as well-known entities, diagnostic problems or cases which may benefit from early diagnosis and therapy.

There is a great temptation for a work of this type to become encyclopedic. Brevity and succinctness are preserved, therefore, at some cost, hopefully with more gain than loss. Probably the most striking examples are the chapters on infectious diseases and parasitology. In most cases, description of clinical syndromes and specific organisms has been eliminated or markedly reduced, because this book is not intended to be a treatise on internal medicine. Emphasis is on material which seems more directly concerned with selection and interpretation of laboratory tests. Nevertheless, a few diseases (such as leptospirosis) are important

from the standpoint of laboratory diagnosis because their signs and symptoms mimic other conditions, so the clinical findings are included in some detail. On the other hand, syphilis serology has a chapter to itself due to confusion which surrounds the multiplicity of available tests. Likewise, certain subjects are discussed at unusual length. These are topics which, in my experience, seem to be common problem areas. The aim is to provide a reasonably thorough, yet compact survey of laboratory medicine. This book is meant to provide some area of assistance to anyone who is engaged in clinical medicine, and to provide, in a sense, a reasonably comprehensive course in clinical pathology.

It is anticipated that the style and format of this book may be criticized; either because the uninitiated reader might gain an impression that laboratory medicine can be reduced to a relatively few rules or protocols, or that one approach to diagnosis is presented as though all others were invalid. Such inferences are not intended.

It should be obvious that no person could write a book covering clinical pathology entirely from his own experience. On the other hand, adequate citation of references would be a tremendous undertaking in itself. A compromise is therefore offered. At the ends of the chapters there are lists of suggested readings, composed of selected references which include textbooks with general or specific coverage, papers on certain specific subjects and occasionally an article selected because of an unusually inclusive bibliography. Due to space considerations, those references with more than two authors have been listed in the first author's name only. This book is only a beginning; the reader is urged to consult these papers and others on individual subjects in order to broaden the information presented here, and to evaluate contrasting points of view.

An Appendix is provided, in order to include certain information which is useful but which seemed better presented separately from the regular text. Much of this is in tabular form.

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Richard Ravel, M.D.

PREFACE TO THE FIFTH EDITION

This book was written to provide as much information as possible that can help in understanding, selecting, and interpreting laboratory tests for patient care. In this edition I have used a slightly different format in order to help find each test more quickly and locate certain information about the different tests more easily. Once again, whenever possible I have included approximate expected percentages from the literature when discussing the frequency of an abnormal test result in a particular disease. Most textbooks state that a test value is either "increased" or "decreased" in a certain disease or that it is increased or decreased "sometimes," "frequently," or "usually." One then reviews the literature and finds that "usually" may represent 60% of cases: that is, 40% of patients have normal test results. This means that an abnormal test result will not be present in a large number of patients and that a normal result is meaningless. Without this knowledge, one might assume that "is increased in" or "usually increased" means "almost always." I think that this information can be extremely useful, and hope that the frequent appearance of these numbers is not annoying or overwhelming. In most cases, I have included the range of test result percentages I found in the literature in order to provide a better evaluation of the approximate expected percentage or the percentage found in some individual report in the literature. One frequently finds that the data from one article may not be representative of what can be expected from the majority of laboratories.

All areas of this book have been completely updated and many sections have been rewritten. More than 50 tests have been added since the previous edition. Some examples (not a complete listing) include: HIV and HTLV virus infection; AIDS and tests for HIV antigen and antibody; delta hepatitis; nucleic acid ("DNA") probes; *Campylobacter pyloridis*; Lyme disease; *Cryptosporidium*; coagulation proteins C and S; "lupus anticoagulant" and antiphospholipid antibodies; D-dimer assay; RBC distribution width measurements; CPK-MM isoforms; fructosamine assay; microalbuminuria in diabetics; bentiromide (PABA) test of pancreatic function; hydrogen breath test in lactase deficiency; clonidine stimulation in pheochromocytoma and in growth hormone testing; ultrasensitive TSH assays; tests for circulating immune complexes; revised FAB criteria for myelodysplastic syndromes; chromosome abnormalities in leukemia (including the bcr gene rearrangement assay); lymphocyte immunotyping; flow cytometry; prostate-specific antigen; cancer antigens 19-9, 15-3, 125, and 549; detection of cocaine, marijuana, and nicotine; digoxin antibody fragment therapy; cyclosporine and tricyclic antidepressent assay; and the NIH Consensus and NCEP criteria for hypercholesterolemia.

Richard Ravel, M.D.

CONTENTS

1 Interpretation of Laboratory Test Data

Interpretation of laboratory test results is much more complicated than simply comparing the test result against a so-called normal range, labeling the test values normal or abnormal according to the normal range limits, and then fitting the result into patterns that indicate certain diseases. Certain basic considerations underlie interpretation of any test result and often are crucial when one decides whether a diagnosis can be made with reasonable certainty or whether a laboratory value should alter therapy.

SENSITIVITY AND SPECIFICITY

All laboratory tests have certain attributes. Sensitivity refers to the ability of the test to detect patients with the disease in question (i.e., how often false negative results are encountered). A test sensitivity of 90% for disease Z indicates that in 10% of patients with disease Z, the disease will not be detected. Specificity describes how well test abnormality is restricted to those persons who have the disease in question (i.e., how often false positive results are produced). A specificity of 90% for disease Z indicates that 10% of results suggestive of disease Z will, in fact, not be due to disease Z.

PREDICTIVE VALUE

In recent years, Galen and Gambino have popularized the concept of predictive value, formulas based on Bayes' theorem that help demonstrate the impact of disease prevalence on interpretation of laboratory test results (Table 1–1). *Prevalence* is the incidence of the disease (or the number of persons with the disease) in the population being tested. Briefly, predictive value helps dramatize the fact that the smaller the number of persons with a certain disease in the population being tested, the lower will be the proportion of persons with an abnormal test result who will be abnormal because they have the disease in question (i.e., the higher will be the proportion of false positive results). For example, if test Y has a sensitivity of 95% and a specificity of 95% for disease Z (both of which would usually be considered quite good), and if the prevalence of disease Z in the general population is 0.1% (1 in 1,000 persons), the predictive value of a positive (abnormal) result will be 1.9%. This means that of 100 persons with abnormal test results, only 2 will have disease Z, and 49 of 50 abnormal test results will be false positive. On the other hand, if the prevalence of disease Z were 10% (as might happen in a group of persons referred to a physician's office with symptoms suggesting disease Z), the predictive value would rise to 68%, meaning that 2 out of 3 persons with abnormal test results would have disease Z.

Predictive value may be applied to any laboratory test to evaluate the reliability either of a positive (abnormal) or a negative (normal) result. Predictive value is most often employed to evaluate a positive result; in that case the major determinants are the incidence of the disease in question for the population being tested and the specificity of the test. However, predictive value is not the only criterion of laboratory test usefulness and may at times be mis-

TABLE 1–1.

Influence of Disease Prevalence on Predictive Value of a Positive Test Result*

Prevalence of Disease in Population Tested (%)	Predictive Value (%) for Test With 95% Sensitivity and 95% Specificity
1	16
5	50
10	68
20	83
50	95

*Percentage of patients with a positive test result who actually have the disease being tested for.

leading if used too rigidly. For example, a test may have excellent characteristics as a screening procedure in terms of sensitivity, low cost, and ease of technical performance and may also have a low positive predictive value. Whether or not the test is useful would depend on other factors, such as the type and cost of follow-up tests necessary in case of an abnormal result and the implications of missing a certain number of persons with the disease if some less sensitive test were employed.

There may be circumstances in which predictive value is misleading or difficult to establish. If one is calculating the predictive value of a test, one must first know the sensitivity and specificity of that test. This information requires that some accurate reference method for diagnosis must be available other than the test being evaluated, that is, a standard against which the test in question can be compared (a gold standard). This may not be possible. There may not be a more sensitive or specific test or test combination available; or the test being evaluated may itself be the major criterion by which the diagnosis is made. In other words, if it is not possible to detect all or nearly all patients with a certain disease, it will not be possible to provide a truly accurate calculation of sensitivity, specificity, or predictive value for tests used in the diagnosis of that disease. The best one could obtain are estimates, which vary in their reliability.

REPRODUCIBILITY AND ACCURACY

Reliability of laboratory tests is quite obviously affected by technical performance within the laboratory. The effect of these technical factors is reflected by test reproducibility and accuracy. Reproducibility (precision or inherent error) is a measure of how closely the laboratory can approach the same answer when the test is performed repeatedly on the same specimen. Theoretically, exactly the same answer should be obtained each time, but in actual practice this does not happen due to equipment and human imperfection. These deviations from the same answer are usually random and thereby form a random or gaussian distribution (Fig 1–1). Variation from the average (mean) value is expressed in terms of standard deviation (SD). The laboratory frequently converts the standard deviation figure to a percentage of the mean value and calls this the coefficient of variation (CV). The majority of tests in a good laboratory can be shown to have reproducibility—expressed as coefficient of variation—in the neighborhood of 4% (some may be a little better and some a little worse). This means that two thirds of the values obtained are actually somewhere between 4% above and 4% below the true value. Since ±2 SD (which includes 95% of the values) is customarily used to define acceptable limits (just as in determination of normal ranges), plus or minus twice the CV similarly forms the boundaries of permissible technical error. Returning to the 4% CV example, a deviation up to ±8% would therefore be considered technically acceptable. In some assays, especially if they are very complicated and automated equipment cannot be used, variations greater than ±8% must be permitted. The experience and integrity of the technical personnel, the reagents involved, and the equipment used all affect the final result and influence reproducibility expressed as CV. In general, one can say that the worse the reproducibility (as reflected in higher CVs), the less chance for accuracy (the correct result), although good reproducibility by itself does not guarantee accuracy.

These considerations imply that a small change in a test value may be difficult to evaluate since it could be due to laboratory artifact rather than to disease or therapy. Larger alterations or a continued sequence of change are much more helpful.

Accuracy is defined as the correct answer (the result or value the assay should produce). Besides inherent error, there is the possibility of unexpected error of various kinds, such as human mistake when obtaining the specimen, performing the test, or transcribing the result.

Investigators have reported erroneous results in 0.2%–3.5% of reports from one or more areas of the laboratory. The laboratory analyzes so-called control specimens (which have known assay values of the material to be tested) with each group of patient specimens. The assumption is that any technical factor that would produce erroneous patient results would also produce control specimen results different from the expected values. Unfortunately, random inaccuracies may not affect all of the specimens and thus may not alter the control specimens. Examples of such problems are a specimen from the wrong patient, the effect of specimen hemolysis or lipemia, inaccurate pipetting, and insufficient mixing when the assay method uses a whole blood specimen. In addition, clerical errors occasionally occur. In my experience, the majority of clerical difficulties are associated with patients who have the same last name, patients who have moved from one room to another, decimal point mistakes, transcription of results onto the wrong person's report sheet, and placement of one person's report sheet into the chart of someone else. These considerations imply that unexpected laboratory abnormalities (or sometimes even the degree of abnormality) should be interpreted in the context of the clinical picture. This does not imply that unexpected test values should be ignored, but if there is doubt, or if the result would call for extensive workup or therapeutic action, it may be advisable to have the test repeated. If possible, the repeat should be performed on the original specimen or, if that is no longer available, on a new specimen obtained without delay. The more time lapse between the original and the new specimen, the more problem in differentiating an error in the original specimen from true change that occurred before the next specimen. One of the more frustrating duties of a laboratory director is to receive a question or complaint about a laboratory test result several days or even weeks after the test was performed, when it is usually too late for a proper investigation.

NORMAL RANGES

The most important single influence on laboratory test interpretation is the concept of

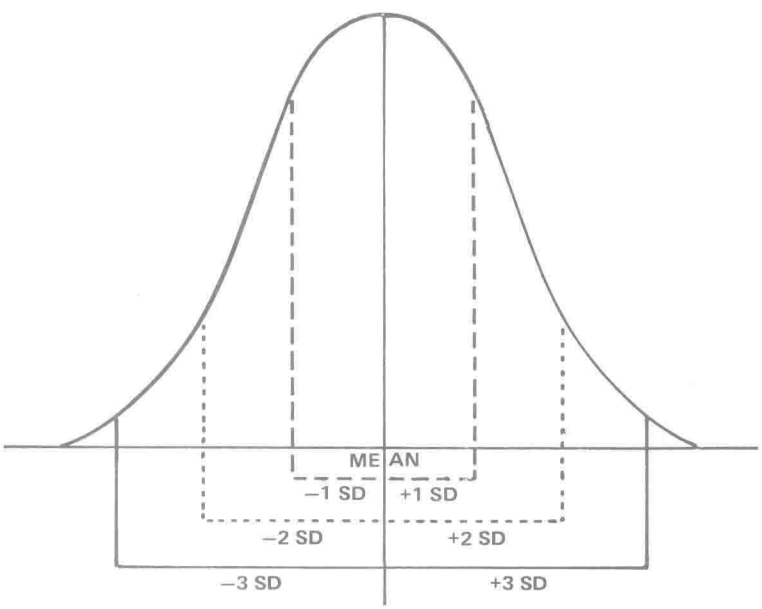

FIG 1–1.
Gaussian (random) value distribution with a visual display of the area included within increments of standard deviation *(SD)* above and below the mean: ± 1 SD = 68% of total values; ± 2 SD = 95% of total values; ± 3 SD = 99.7 % of total values.

a normal range, within which test values are considered normal and outside of which they are considered abnormal. The criteria and assumptions used in differentiating normal from abnormal in a report, therefore, assume great importance. The first step usually employed to establish normal ranges is to assume that all persons who do not demonstrate clinical symptoms or signs of any disease are normal. For some tests, normal is defined as no clinical evidence of one particular disease or group of diseases. A second assumption commonly made is that test results from those persons considered normal will have a random distribution; in other words, no factors that would bias a significant group of these values toward either the low or the high side are present. If the second assumption is correct, a gaussian (random) distribution would result, and a mean value located in the center (median) of the value distribution would be obtained. Next, the average deviation of the different values from the mean (SD) can be calculated. In a truly random or gaussian value distribution, 68% of the values will fall within 1 SD above and below the mean, 95% within ±2 SD, and 99.7% within ±3 SD (see Fig 1–1). The standard procedure is to select ±2 SD from the mean value as the limits of the normal range.

Accepting ±2 SD from the mean value as normal will place 95% of clinically normal persons within the normal range limits. Conversely, it also means that 2.5% will have values above and 2.5% will have values below this range. Normal ranges created in this way represent a deliberate compromise. A wider normal range (e.g., ±3 SD) would ensure that almost all normal persons would be included within normal range limits and thus would increase the specificity of abnormal results. However, this would place additional diseased persons with relatively small test abnormality into the expanded normal range and thereby decrease test sensitivity for detection of disease.

Problems Derived From Use of Normal Ranges

1. A small but definite group of clinically normal persons may have subclinical or undetected disease and may be inadvertently included in the supposedly normal group used to establish normal values. This has two consequences. There will be abnormal persons whose laboratory value will now be falsely considered normal, and the normal limits may be influenced by the values from persons with unsuspected disease, thereby extending the normal limits and accentuating overlap between normal and abnormal persons. For example, we tested serum specimens from 40 clinically normal blood donors to obtain the normal range for a new serum iron kit. The range was found to be 35–171 μg/dl, very close to the values listed in the kit package insert. We then performed a serum ferritin assay (the current gold standard for iron deficiency, see chapter 3) on the 10 serum samples with the lowest serum iron values. Five had low ferritin levels suggestive of iron deficiency. After excluding these values, the recalculated serum iron normal range was 60–160, very significantly different from the original range. The kit manufacturer conceded that their results had not been verified by serum ferritin or bone marrow.

2. Normal ranges are sometimes calculated from a number of values too small to be statistically reliable.

3. Various factors may affect results in nondiseased persons. The population from which specimens are secured for normal range determination may not be representative of the population to be tested. There may be differences due to age (see Table 36–1), sex, locality, race, diet, posture (Table 1–2), specimen storage time, and so forth. An example is the erythrocyte sedimentation rate (ESR) in which the normal values by the Westergren method for persons under age 60 years, corrected for ane-

TABLE 1–2.

Decrease in Test Values After Change From Upright to Supine Position*

Test	% Decrease
Hemoglobin	4 (0–17)
Hematocrit	6 (4–9)
Potassium	1 (0–3)
Calcium	4 (2–6.8)
Total protein	9 (7–10)
Albumin	9 (6.2–14)
Cholesterol	9 (5–15)
Triglyceride	10 (3–20)
Alkaline phosphatase	9 (5–11)
Alanine aminotransferase (SGPT)	7 (4–14)

*Average percent change with range of values found in the literature.

mia, are 0–15 mm/hour for men and 0–20 mm/hour for women, whereas in persons over age 60, normal values are 0–25 mm/hour for men and 0–30 mm/hour for women. There may even be significant within-day or between-day variation in some substances in the same person.

4. Normal values obtained by one analytical method may be inappropriately used with another method. For example, there are several well-accepted techniques for assay of serum albumin. The assay values differ somewhat because the techniques do not measure the same thing. Dye-binding methods measure dye-binding capacity of the albumin molecule, biuret procedures react with nitrogen atoms, immunologic methods depend on antibodies against antigenic components, and electrophoresis is influenced primarily by the electric charge of certain chemical groups in the molecule. In fact, different versions of the same method may not yield identical results, and even the same version of the same method, when performed on different equipment, may display variance.

5. As pointed out previously, normal values supplied by the manufacturers of test kits rather frequently do not correspond to the results obtained on a local population by a local laboratory, sometimes without any demonstrable reason. The same problem is encountered with normal values obtained from the medical literature. In some assays, such as fasting serum glucose using so-called true glucose methods, there is relatively little difference in normal ranges established by laboratories using the same method. In other assays there may be a significant difference. For example, one reference book suggests a normal range for serum sodium by flame photometry of 136–142 mEq/L, whereas another suggests 135–155 mEq/L. A related problem is the fact that normal ranges given in the literature may be derived from a laboratory or group of laboratories using one equipment and reagent system, whereas results may be considerably different when other equipment and reagents are used. The only way to compensate for this would be for each laboratory to establish its own normal ranges. Since this is time-consuming, expensive, and a considerable amount of trouble, it is most often not done; and even laboratories that do establish their own normal ranges are not able to do so for every test.

6. Population values may not be randomly distributed and may be skewed toward one end or the other of the range. This would affect the calculation of standard deviation and distort the normal range width. In such instances, some other way of establishing normal limits, such as a nonparametric method, would be better, but this is rarely done in most laboratories.

One can draw certain conclusions about problems derived from the use of the traditional concept and construction of normal ranges:

1. Some normal persons may have abnormal laboratory test values. This may be due to ordinary technical variables. An example is a person with a true value just below the upper limit of normal that is lifted just outside of the range by laboratory method imprecision. Another difficulty is the 2.5% of normal persons arbitrarily placed both above and below normal limits by using ± 2 SD as the limit criterion. It can be mathematically demonstrated that the greater the number of tests employed, the greater the chance that at least one will yield a falsely abnormal result. In fact, if a physician uses one of the popular 12-test biochemical profiles, there is a 46% chance that at least one test result will be falsely abnormal. Once the result falls outside normal limits, without other information there is nothing to differentiate a truly abnormal from a falsely abnormal value, no matter how small the distance from the upper normal limit. Of course, the farther the values are from the normal limits, the greater the likelihood of a true abnormality. Also, if two or more tests that are diagnosis-related in some way are simultaneously abnormal, it reinforces the probability that true abnormality exists. Examples could be elevation of aspartate aminotransferase (SGOT) and alkaline phosphatase levels in an adult nonpregnant woman, a combination that suggests liver disease, or elevation of both blood urea nitrogen (BUN) and creatinine levels, which occurring together strongly suggest a considerable degree of renal function impairment.

2. Persons with disease may have normal test values. Depending on the width of the normal range, considerable pathologic change in the assay value of any individual person may occur without exceeding normal limits of the population. For example, if the person's test value is normally in the lower half of the population limits, his or her test value might double or undergo even more change without

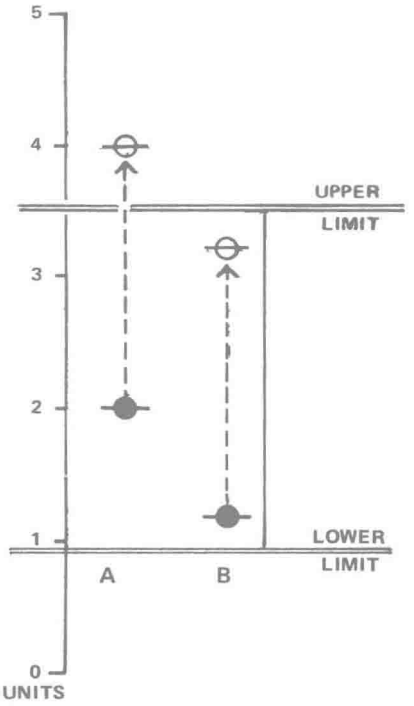

FIG 1–2.
How patient abnormality may be hidden within population reference ("normal") range. Patients A and B had the same degree of test increase, but the new value for patient B remains within the reference range because the baseline value was sufficiently low.

exceeding population limits (Fig 1–2). Comparison with previous baseline value would be the only way to demonstrate that substantial change had occurred.

Due to the various considerations outlined previously, there is a definite trend toward avoiding the term "normal range." The most frequently used replacement term is *reference range* (or *reference limits*). Therefore, the term "reference range" will be used throughout this book instead of "normal range."

PROBLEMS WITH LABORATORY SPECIMENS

Specimen collection and preservation may create laboratory problems (see Table 36–40). Probably the most frequent offender is contamination of urine from female patients by vaginal or labial secretions. Using more than 10 squamous epithelial cells per low-power field in a centrifuged urine sediment as the index of probable contamination, my surveys have found this present in 20%–30% of female random voided or midstream ("clean catch") specimens. These secretions may add red blood cells, white blood cells, protein, and bacteria to the urine. Nonfasting blood specimens may occasionally be troublesome, particularly for blood glucose and the effect of lipemia. This is most frequent in patients who are admitted in the afternoon and in outpatients. We have had some success in alleviating this problem by requesting that physicians ask elective presurgical patients either to have admission laboratory tests drawn fasting prior to admission or to come to the hospital for admission after fasting at least 3 hours. Certain tests, such as blood gas analysis, biochemical acid phosphatase assay, and plasma renin assay, necessitate special preservation techniques to be reliable.

One of the most well-known specimen collection problems is that of ensuring completeness of 24-hour urine specimens. Some patients are not informed that the 24-hour collection begins only after a urine specimen has been voided and discarded. It is frequently helpful to give the patient written instructions as to how a clean-voided specimen may be obtained and how the 24-hour specimen is collected. The two standard criteria used to evaluate adequacy of collection are the specimen volume and the urine creatinine content. Specimen volume is helpful only when the volume is abnormally low (e.g., <400 ml/24 hours in adults). A small volume that does not have maximal concentration (as evidenced by a high specific gravity or osmolality) suggests incomplete collection. However, renal disease, medications such as diuretics, and other conditions may prevent concentration, so this criterion is difficult to apply unless the patient is known to have good renal function. The second criterion is a normal quantity of urine creatinine. Creatinine is derived from muscle metabolism and has a reasonably constant daily excretion. However, creatinine production and excretion are dependent on body muscle mass. It has also been shown by several investigators that even in the same individual, daily creatinine excretion may vary 5%–25%, with an average variation of about 10%. Meat, especially when cooked for a long time, may increase creatinine

excretion up to 40% for short periods of time and possibly 10%–20% over a 24-hour period.

Since creatinine excretion correlates with muscle mass, it might be helpful to compare measured creatinine excretion with calculated ideal excretion based on body height and ideal body weight (see Table 36–19). This would be only a rough benchmark, but it might be more helpful than the population reference range, which is rather wide.

EFFECTS OF PHYSIOLOGIC VARIABLES

Physiologic differences between groups of persons may affect test results. These deviations may be attributable to normal metabolic alterations in certain circumstances. Some examples are age (e.g., an increase in alkaline phosphatase levels in children compared with adult values) (see Table 36–1), sex (e.g., higher values for serum uric acid in males than in females), race (e.g., higher values for creatine phosphokinase in black men than in white men); time of day (e.g., higher values for serum cortisol in the morning than in the evening), meals (e.g., effect on blood glucose), and body position (e.g., change in values shown in Table 1–2 due to change in posture, resulting in possible decrease in many serum test values when an ambulatory outpatient becomes a hospital inpatient).

EFFECTS OF MEDICATIONS

The effect of medications is a major problem since a patient may be taking several drugs or may be taking over-the-counter pharmaceuticals without reporting them to the physician. Medication effects (see Table 36–2) may be manifest in several ways: drug-induced injury to tissues or organs (e.g., isoniazid-induced hepatitis), drug-induced alterations in organ function (e.g., increase in γ-glutamyltransferase produced by phenytoin microsomal induction in liver cells), drug competition effect (e.g., displacement of thyroxine from thyroxine-binding proteins by phenytoin), and interference by one drug with the analysis method of another (e.g., decrease in serum glucose using glucose oxidase when large doses of vitamin C are ingested).

EFFECTS OF HOSPITAL WORKING PROCEDURES

Several common hospital conditions may affect laboratory results without such alteration being recognized by the physician. These include intravenous fluids running at the time the test specimen is drawn, the effect of dehydration, the effect of heparin flushes on some tests, the effects of various medications, and in certain cases the administration of medication at a time different from that expected or recorded. The last item refers to the common situation in which several patients are scheduled to receive medication at the same time (e.g., 8 A.M.). Although administration to each may be charted as being the same time,the actual time that any individual receives the medication may vary significantly.

Another frequent problem is defective communication between the physician and the laboratory. In some cases this takes the form of incorrectly worded, ambiguous, or illegible orders. Nursing or secretarial personnel can easily misinterpret such orders and relay them incorrectly to the laboratory. Nonstandard test abbreviations or acronyms created from the names of new tests not familiar to nursing personnel also cause difficulties. In some cases the physician should supply at least a minimal amount of pertinent clinical information to obtain better service. This information is most vitally needed in the microbiology department. The microbiology technologist must know from what area the specimen was obtained, exactly what type of culture is desired, and especially, whether any particular organism is suspected so that special growth media or special handling may be employed if necessary. Basic clinical information is even more essential to the surgical pathologist and the radiologist. The surgical pathologist must at least know where the tissue specimen originated, and both the pathologist and radiologist can do a much better job providing an answer to the clinician if they could only know what the clinician's question is (i.e., for what reason is he or she requesting the study).

A word must be said about stat orders. *Stat* means emergency to the laboratory. Someone must stop whatever he or she is doing and perform the stat analysis immediately, possibly having to obtain the specimen first. After analysis the report must be delivered immediately.

During this time that laboratory person may not do any other work. Stat tests result in great decrease of laboratory efficiency and cost effectiveness. The most efficient and least expensive way to perform tests is to analyze several patient specimens at the same time, so that the initial setup and quality control portions of the test need be performed only once and all specimens can be incubated simultaneously. Extra speed is obtained when a test is ordered stat, but results for everyone else are delayed. Unfortunately, many stat requests, sometimes even the majority, are ordered for reasons other than a true emergency need for the result. In some cases the order orginates from nursing service because someone neglected to send a requisition for a routine test to the laboratory. In other cases the order is made stat because of convenience to the physician or the patient. Stat orders for these purposes at best are inconsiderate, wasteful, and disruptive. The physician should consider whether some other action-producing order category could be substituted, such as "as soon as possible." If the actual problem is that of unacceptable turnaround time for routine tests, this is a matter to be discussed with the laboratory director rather than evaded by stat orders.

LABORATORY TESTS AND THE MEDICAL LITERATURE

One of the more interesting phenomena in medicine is the scenario under which new tests or new uses for old tests are introduced. In most cases the initial reports are highly enthusiastic. Also in most cases there is eventual follow-up by other investigators who either cannot reproduce the initial good results or who uncover substantial drawbacks to the test. In some cases the problem lies in the fact that there may not be any way to provide an unequivocal standard against which test accuracy can be measured. An example is acute myocardial infarction, because there is no conclusive method to definitively separate severe myocardial ischemia from early infarction (i.e., severe reversible change from irreversible change). Another example is acute pancreatitis. In other cases the initial investigators may use analytical methods (e.g., "homemade" reagents) that are not identical to those of subsequent users. Other possible variances include different populations tested, different conditions under which testing is carried out, and effects of medication. Historical perspective thus suggests that initial highly enthusiastic claims about laboratory tests should be received with some caution.

Additional information relevent to this chapter is found in Chapter 35.

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