PHYSICAL

PHARMACY

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Physical Chemical Principles in the Pharmaceutical Sciences

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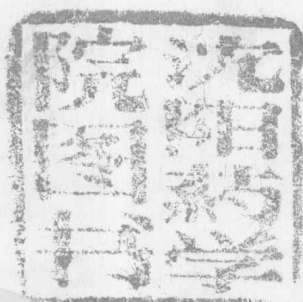
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SECOND EDITION

Preface

Although the basic principles of *Physical Pharmacy* have remained essentially unchanged through the years, advances have occurred in the pharmaceutical sciences since the publication of the first edition in 1960. Typical are the applications of kinetic principles to biopharmaceutics, dissolution rate and emulsion breakdown. The solution of these problems has been assisted greatly by the analog computer. Phase diagrams and the thermodynamics of phase equilibria are now being used by the product development pharmacist in the design and manufacture of stable emulsions and solubilized products. A new graphical treatment of ionic equilibria has permitted the study of complex mixtures of ionic species in pharmaceutical solutions. And the steady development of quantum chemistry and computer science has provided new tools for the study of structure-activity relations and is beginning to throw some light on the mysteries of drug-receptor interactions. At the same time, greater utilization of basic principles has taken place in the areas of micromeritics and rheology, and suspensions and emulsions are now being studied in quantitative, rather than qualitative, terms.

The second edition of *Physical Pharmacy* takes note of these advances and presents new material which is designed to keep the student, teacher, and research pharmacist abreast of the burgeoning specialties in pharmaceutics and physical medicinal chemistry.

The authors are indebted to several specialists in various fields of science and mathematics who prepared chapters or sections of chapters. Dr. Paul Niebergall, recognized for his treatment of ionic equilibria, responded graciously to our call for a contribution on the new approach to Ionic Equilibria. Dr. Ronald Wiegand, an established expert in pharmacokinetics, prepared the section of the kinetics chapter dealing with the important subject of biopharmaceutics. The original draft of the chapter on computers was modified and improved by the joint efforts of Mrs. Nancy B. Pierce, Mr. Walter Witschey, Mr. Michael Mulshine, Mr. William Kaplan, Dr. James Zimmerman, and was reviewed by Mr. Paul Sanders and Dr. Robert Brusenback. Dr. Alexander Chun prepared most of the illustrations, as he had done for the first edition. His careful attention to detail and advice on text changes as well as illustrations have helped greatly to make this a better book. Mr. Antino Wood helped to prepare some of the illustrations.

The list of books included as an appendix was revised with the assistance of Mrs. Theodora Andrews and Mr. Seymour

Zelmanoff. Mr. Zelmanoff also helped in checking illustrations and references and in reading proof.

Many friends in pharmacy have sent suggestions for improvements. We are grateful to them and to our colleagues at Purdue University, the Medical College of the Virginia Commonwealth University, Temple University and the University of Connecticut for their advice and assistance. Mr. John Spahr, Mr. Martin Dallago and Mr. Thomas Colaiezzi of Lea & Febiger have been most sympathetic and helpful during the revision of the book.

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Contents

1

Physical and Mathematical Fundamentals

INTRODUCTION

The pharmacist today, more than ever before, is called upon to demonstrate a sound knowledge of pharmacology, organic chemistry, and an intelligent understanding of the physical and chemical properties of the new medicinal products which he prepares and dispenses.

Whether engaged in research, teaching, manufacturing, retail pharmacy or any of the allied branches of his profession, the pharmacist must recognize the need for borrowing heavily from the basic sciences. This stems from the fact that pharmacy is an applied science, composed of principles and methods that have been culled from the other disciplines. The pharmacist who is engaged in advanced studies must work at the boundary between the various sciences, and he must keep abreast of advances in the physical, chemical and biological fields if he is to understand and contribute to the rapid developments in his own profession.

Pharmacy, like many other applied sciences, has passed through a descriptive and an empirical era and is now entering the quantitative and theoretical stage.

The scientific principles of pharmacy are not so complex as some would believe, and certainly they are not beyond the understanding of the well-educated pharmacist of today. In the following pages the reader will be directed through fundamental theory and experimental findings to practical conclusions in a manner which should be followed easily by the average upperclass pharmacy student.

The name *physical* or *theoretical* pharmacy has been associated with the area of pharmacy that deals with the quantitative and theoretical principles of science as they apply to the practice of pharmacy. Physical pharmacy attempts to integrate the factual knowledge of pharmacy through the development of broad principles of its own, and it aids the pharmacist, the pharmacologist and the pharmaceutical chemist in their attempt to predict the solubility, stability, compatibility, and the rate of absorption and duration of action of drug products. As a result of this knowledge, the pharmaceutical scientist is in a better position to develop new drugs and dosage forms and to improve upon the various modes of administration.

CONCEPTS AND METHODS OF SCIENCE

The reader was no doubt introduced to the *Scientific Method* in general chemistry. Much has been written and said about this "method." Some philosophers and scientists, perhaps the most famous of whom was Aristotle, have suggested that there is a series of well-ordered steps by which the scientist proceeds to attack and solve problems. Others, however, have doubted the existence of the method. They argue that the scientist uses no magic formula which is not also available to the businessman and to the housewife for confronting and solving their daily problems. Darlington, an English geneticist, has asserted that science does not progress like a steamroller, crushing each problem that falls in its path and compressing it into its proper place. Instead, it behaves like a sticking drawer which gives on one side and then jams on the other.

We shall not attempt to settle the question of whether scientific investigation proceeds in an orderly array of techniques and methods, or in a haphazard process of trial and error with no holds barred. However, we can perhaps shed some light on the workings of science by considering in a general way some of the tasks in which the scientist engages. These include: observing phenomena and forming tentative approaches and solutions known as *hypotheses;* experimenting and arranging the data in an orderly manner so as to form generalizations, preferably mathematical relationships or *laws;* combining these laws into a unified *theory* so as to "explain" the nature of the relationships

and predict new phenomena and regularities in nature; and finally verifying the theory by further experimentation. In addition to careful experimentation and thought on the part of the researcher, the program usually calls for a greater or lesser amount of creative imagination and ingenuity in suggesting tentative hypotheses, in organizing the data into generalizations and mathematical laws, and in the development of theories.

If one would watch an average investigator as he proceeded to solve a scientific problem, he might observe the following stages. More than likely the scientist would approach a totally new problem by the method of trial-and-error. As he developed a clearer understanding of the problem through continued experimentation and began to recognize certain relationships among the elements, the investigator would pass from the early exploratory phases through a succession of increasingly ordered and planned stages of research. Finally, when conclusions checked with experimental results the scientist would be well along the way to a satisfactory solution to the problem.

The student should pause at this point in the development of the subject to consider methods by which Physical Pharmacy can be made both interesting and worthwhile.

This course should mark the turning point in the study pattern of the advanced student, for in the latter part of the pharmacy curriculum emphasis is placed upon the application of scientific principles to practical professional problems. Although facts must be the foundation upon which any body of knowledge is built, the rote memorization of disjointed "particles" of knowledge does not lead to logical and systematic thought. The student should strive in this course to integrate facts and ideas into a meaningful whole. In his future career he frequently will call upon these generalizations to solve practical pharmaceutical problems.

The comprehension of course material is primarily the responsibility of the student. The teacher can guide and direct, explain and clarify, but facility in solving problems in the classroom and the laboratory depends largely on the student's understanding of theory, his recall of facts, his ability to integrate knowledge, and his willingness to devote sufficient time and effort to the task. Each assignment should be read and outlined, and assigned problems should be solved outside the classroom. The teacher's comments will then serve to clarify questionable points and aid the learner to improve his judgment and reasoning ability.

DIMENSIONS AND UNITS

The properties of matter are usually expressed by the use of three arbitrarily chosen quantities: length, mass and time. Each of these properties is assigned a definite *unit* and a *reference standard*. In the metric system the units are the centimeter (cm), the gram (g or Gm) and the second (sec); accordingly it is often called the *cgs* system. A reference standard is a fundamental unit relating each measurable quantity to some natural or artifical constant in the universe.

Measurable quantities such as area, density, pressure and energy are compounded from the three fundamental properties referred to above. In carrying out the operation of measurement we assign to each property a dimension which is expressed quantitatively in units. Thus the quantities of length, area and volume are measured in the dimension of length (L), length squared (L^2), and length cubed (L^3), respectively corresponding to the unit of cm, cm² and cm³. The fundamental dimensions and units are given in Table 1-1.

Length and Area. The dimension of length serves as a measure of distance and has as its reference standard the *meter*. It is defined as

$$1 \text{ meter} = 1.65076373 \times 10^6 \lambda_{\text{Kr-86}}$$

where $\lambda_{\text{Kr-86}} = 6.0578021 \times 10^{-7}$ m is the wave length in vacuo of the transition between two specific energy levels of the krypton-86 atom. Prior to this definition, the

TABLE 1-1. Fundamental Dimensions and Units

Measurable Quantity	Dimensional Symbol	Cgs Unit	Reference Standard
Length (l)	L	Centimeter (cm)	Meter
Mass (m)	M	Gram (g or Gm)	Kilogram
Time (t)	T	Second (sec)	Mean solar day

meter was arbitrarily defined as the distance between two lines on a platinum-iridium bar preserved at the International Bureau of Weights and Measures in Sèvres, France. The unit of length, the centimeter (cm), is one-hundredth of a meter, the common divisions and multiples of which are found in general chemistry and pharmacy books. In the microscopic range, lengths are often expressed as microns (μ), millimicrons (mμ) and Angstrom units (A). The micron is equal to 0.001 mm, the millimicron is 0.001 μ, and the Angstrom unit is 0.1 mμ or 10^{-8} cm.

Area is the square of a length and has the unit of square centimeters (sq cm or cm^2).

Volume. The measurable quantity, volume, is also derived from length. Its reference standard is the *cubic meter;* its unit is one-millionth of this value or 1 cubic centimeter (cc or cm^3). Volume was originally defined in terms of the *liter,* the volume of a kilogram of water at 1 atmosphere pressure and 4° C, and was meant to be equivalent to 1000 cc. Owing to the failure to correct for the dissolved air in the water, however, the two units do not compare exactly. It has since been established that 1 liter actually equals 1000.027 cc. Thus, there is a discrepancy between the milliliter (one-thousandth of a liter) and the cubic centimeter, but it is so slight as to be disregarded in general chemical and pharmaceutical practice. Volumes are usually expressed in milliliters (ml) in this book in conformity with the U.S. Pharmacopeia and the National Formulary; however, cubic centimeters are employed sometimes in the text where this notation seems more appropriate.

The pharmacist uses cylindrical and conical graduates, droppers, pipettes and burettes for the measurement of volume; graduates are used more frequently than the other measuring apparatus in the pharmacy laboratory. The flared conical graduate is less accurate than the cylindrical type, and the use of the flared graduate should be discouraged except for some liquids which need not be measured accurately. The selection of the correct graduate for the volume of liquid to be measured has been determined by Goldstein *et al.*[1]

Mass. The standard of mass is the kilogram. It is the mass of a platinum-iridium block preserved at the Bureau of Weights and Measures. The practical unit of mass is the gram (Gm), which is one-thousandth of a kilogram. Mass is often expressed as the weight of a body. The balance is said to be used for "weighing," and the standard masses are known as "weights." The proper relationship between mass and weight will be considered under the topic of force.

In order to weigh drugs precisely and accurately, the pharmacist must understand the errors inherent in operating a balance. A Class A balance, used for the compounding of prescriptions, is serviceable only if kept in good working condition and if checked periodically for equality of arm length, beam rider accuracy, and sensitivity. These tests are described in the booklet by Goldstein and Mattocks.[2] Furthermore, a good balance is of no use unless an accurate set of weights is available.

Density and Specific Gravity. The pharmacist frequently uses these measurable

quantities when interconverting between mass and volume. Density is a derived quantity since it combines the units of mass and volume. It is defined as mass per unit volume at a fixed temperature and pressure and is expressed in the metric system in grams per cubic centimeter (Gm/cm^3).

Specific gravity, unlike density, is a pure number without dimension; however, it may be converted to density by the use of appropriate formulas.[3] Specific gravity is defined as the ratio of the density of a substance to the density of water, the values for both substances being determined at the same temperature unless otherwise specified. The term specific gravity in light of its definition is a poor one; it would be more proper to refer to it as relative density.

Specific gravity is more often defined for practical purposes as the ratio of the mass of a substance to the mass of an equal volume of water at 4° or at some other specified temperature. The following notations are frequently found to accompany specific gravity readings: 25°/25°, 25°/4° and 4°/4°. The first figure refers to the temperature of the air in which the substance was weighed; the figure following the slant line is the temperature of the water used. The official pharmaceutical compendia use a basis of 25°/25° for expressing specific gravity.

Specific gravity may be determined by the use of various types of pycnometers, the Mohr-Westphal balance, hydrometers and other devices. The measurements and calculations are discussed in elementary chemistry, physics and pharmacy books.

Other Dimensions and Units. The derived dimensions and their units are listed in Table 1-2. Although the units and relations are self-explanatory for most of the derived dimensions, force, pressure and energy require some elaboration.

Force. One is familiar with force in everyday experience as a push or pull required to set a body in motion. The larger the mass of the body and the greater the required acceleration, the greater is the force that one must exert. Hence, the force is directly proportional to the mass (when acceleration is constant) and to the acceleration (when the mass is constant). This may be represented by the relation,

$$\text{Force} \propto \text{Mass} \times \text{Acceleration} \quad (1)$$

This proportionality is converted to an equality, *i.e.*, to an equation or mathematical expression involving an equal sign, according to the laws of algebra by the introduction of a constant. Accordingly, we write

$$f = k \times m \times a \quad (2)$$

in which f is the force, k is the *proportionality constant*, m is the mass and a is the acceleration. If the units are chosen so that the constant becomes unity, *i.e.*, has the

TABLE 1-2. Derived Dimensions and Units

Measurable Quantity	Dimension	Cgs Unit	Relationship to Other Dimensions
Area (A)	L^2	cm^2	the square of a length
Volume (V)	L^3	cm^3	the cube of a length
Density (ρ)	ML^{-3}	Gm/cm^3	mass/unit volume
Velocity (v)	LT^{-1}	cm/sec	length/unit time
Acceleration (a)	LT^{-2}	cm/sec^2	length/(time)^2
Force (f)	MLT^{-2}	$Gm\ cm/sec^2$ or dyne	mass $\times$ acceleration
Pressure (p)	$ML^{-1}T^{-2}$	$dyne/cm^2$	force/unit area
Energy (E)	ML^2T^{-2}	$Gm\ cm^2/sec^2$ or erg	force $\times$ length

value of 1, the well-known force equation of physics is obtained:

$$f = m \times a \qquad (3)$$

The unit of force is the *dyne,* defined as that force which imparts to a mass of 1 gram an acceleration of 1 cm/sec^2.

The reader should recall from physics that weight is the force of gravitational attraction that the earth exerts on a body, and it properly should be expressed in force units (dynes) rather than mass units (grams). The relationship between weight and mass can be obtained from equation (3). Substituting weight w for force and g for acceleration, the equation becomes

$$w = m \times g \qquad (4)$$

Although the gravitational acceleration of a body varies from one part of the earth to another, it is approximately constant at 981 cm/sec^2. Substituting this value for g, the weight of a 1 gram mass is calculated from equation (4) as follows:

$$w = 1 \, \text{Gm} \times 981 \, \text{cm/sec}^2$$

and

$$w = 981 \, \text{Gm cm/sec}^2 \, \text{or} \, 981 \, \text{dynes}$$

Therefore, the weight of a body with a mass of 1 gram is actually 981 dynes. It is common practice to express weight in the mass unit, grams, since weight is directly proportional to mass; however in problems involving these physical quantities, the distinction must be made.

Pressure. *Pressure* may be defined as force per unit area; the unit commonly used in science is dyne/cm^2. Pressure is often given in atmospheres (atm), or in centimeters or millimeters of mercury. This latter unit is derived from a measurement of the height of a column of mercury in a barometer which is used to measure the atmospheric pressure. At sea level the mean pressure of the atmosphere supports a column of mercury 76 cm (760 mm) in height. The barometric pressure may be translated into the fundamental pressure unit, dyne/cm^2, by multiplying the height times 1 cm^2 cross sectional area by the density of mercury, 13.595 Gm/cm^3, at 0° to give the mass and multiplying this by the acceleration of gravity, 980.7 cm/sec^2. The result divided by cm^2 is 1.0133×10^6 dyne/cm^2 and is equal to 1 atm.

Work and Energy. Energy is frequently defined as the condition of a body which gives it the capacity for doing work. The concept actually is so fundamental that no adequate definition can be given. Energy may be classified as kinetic energy or potential energy.

The idea of energy is best approached by way of the mechanical equivalent of energy known as *work* and the thermal equivalent of energy or *heat.* When a constant force is applied to a body in the direction of its movement, the work done on the body equals the force multiplied by the displacement, and the system undergoes an increase in energy. The product of force and distance has the same dimensions as energy, namely ML^2T^{-2}. Other products also having the dimensions of energy are pressure $\times$ volume, surface tension $\times$ area, mass $\times$ velocity^2, and potential difference $\times$ quantity of electricity.

The cgs unit of work, also the unit of kinetic and potential energy, is the erg. It is defined as the work done when a force of 1 dyne acts through a distance of 1 centimeter:

$$1 \, \text{erg} = 1 \, \text{dyne} \times 1 \, \text{cm}$$

The erg is often too small for practical use and is replaced by the absolute joule (pronounced *jewel*) which is equal to 10^7 ergs:

$$1 \, \text{absolute joule} = 1 \times 10^7 \, \text{erg}$$

In carrying out calculations in the cgs system involving work and pressure, work must be expressed in ergs and pressure in dynes/cm^2. When using any other system, consistent units must also be employed.

Heat and work are equivalent forms of energy and are interchangeable under certain circumstances. The thermal unit of energy is the gram calorie (small calorie).

It was formerly expressed as the amount of heat necessary to raise the temperature of 1 gram of water from 15° to 16° C. The small calorie is now defined as equal to 4.184 absolute joules. The large or kilogram calorie (kcal) equals 1000 small calories.

Temperature is assigned a unit known as the degree. On the centigrade and the Kelvin or absolute scales, the freezing and boiling points of pure water at 1 atm pressure are separated by 100 degrees. Zero degrees on the centigrade scale equals 273.16° on the Kelvin scale.

SOME ELEMENTS OF MATHEMATICS

The student should become familiar with the fundamental concepts of mathematics which are frequently employed in the physical sciences and upon which are based many of the equations and graphical representations encountered in the remainder of the book. The fundamentals of calculus are found in the next chapter.

Calculations Involving Dimensions. Ratio and proportions are frequently used in the physical sciences for conversions from one system to another. The following calculation illustrates the use of proportions.

Example 1. How many gram calories are there in 3.00 joules? One should first recall a relationship or ratio that connects calories and joules. The relation, 1 cal = 4.184 joules, comes to mind. The question is then asked in the form of a proportion: "If 1 calorie equals 4.184 joules, how many calories are there in 3.00 joules?" The proportion is set down, being careful to express each quantity in its proper units. For the unknown quantity, an "X" is used.

$$\frac{1 \text{ cal}}{4.184 \text{ joules}} = \frac{X}{3.00 \text{ joules}}$$

$$X = \frac{3.00 \text{ joules} \times 1 \text{ cal}}{4.184 \text{ joules}}$$

$$X = 0.717 \text{ cal}$$

A second method, based on the requirement that the units as well as the dimensions must be identical on both sides of the equal sign, is sometimes more convenient than the method of proportions.

Example 2. How many gallons are equivalent to 2.0 liters? It would be necessary to set up successive proportions in order to solve this problem. In the method involving identity of dimensions on both sides of the equation, the quantity desired X (gallons) is placed on the left and its equivalent, 2.0 liters, is set down on the right side of the equation. The right side must then be multiplied by known relations in ratio form, such as 1 pint per 473 ml, to give the units of gallons. Carrying out the operations indicated yields the result with its proper units.

$$X = 2.0 \text{ liters} \times (1000 \text{ ml/liter})$$
$$\times (1 \text{ pt}/473 \text{ ml}) \times (1 \text{ gal}/8 \text{ pt})$$
$$X = 0.53 \text{ gal}$$

One may be concerned about the apparent disregard for the rules of significant figures (p. 13) in the equivalents such as 1 pint = 473 ml. The quantity of pints can be measured as accurately as the milliliters, so that we assume 1.00 pint is meant here. The quantities 1 gallon and 1 liter are also exact by definition, and significant figures need not be considered in such cases.

Exponents. The various operations involving exponents, that is the powers to which a number is raised, are best reviewed by studying the examples set out in Table 1-3.

Logarithms. The equality

$$10^3 = 1000 \tag{5}$$

is expressed in logarithmic notation as:

$$\log_{10} 1000 = 3 \tag{6}$$

The exponent 3 to which the base 10 is raised to give 1000 in equation (5) is referred to as the logarithm of 1000. The number 1000 is known as the *antilogarithm* of the number 3. In general, if b, raised to the power x, gives the number a, then the logarithm to the base b of a is x:

$$b^x = a \tag{7}$$

$$\log_b a = x \tag{8}$$

TABLE 1-3. The Rules of Exponents

$a \times a \times a = a^3$	$a^2/a^4 = a^{2-4} = a^{-2} = \dfrac{1}{a^2}$
$a^2 \times a^3 = a^{2+3} = a^5$	$a^2/a^2 = a^{2-2} = a^0 = 1$
$(a^2)^3 = a^2 \times a^2 \times a^2 = a^6$	$a^{1/2} = \sqrt{a}$
$\left(\dfrac{a}{b}\right)^3 = a^3/b^3$	$a^{1/2} \times a^{1/2} = a^{1/2+1/2} = a^1 = a$
$a^5/a^2 = a^{5-2} = a^3$	$a^{2/3} = (a^2)^{1/3} = \sqrt[3]{a^2}$
$a^5/a^4 = a^{5-4} = a^1 = a$	

When 10 is used as the base the logarithm is known as the *common* or *Briggsian* logarithm, whereas the number 2.71828 . . . , designated as *e*, is used as the base for the *natural* or *Napierian* logarithms. The quantity *e* is important in the theoretical development of the physical and biochemical sciences and is discussed in some detail by Daniels.[4] It is the sum of the series $1 + 1 + 1/2! + 1/3! + 1/4! \ldots$ where ! denotes a factorial number which is defined as the product of the positive integers between 1 and the number. Thus $2! = 1 \times 2$, $3! = 1 \times 2 \times 3 = 6$, and $4! = 1 \times 2 \times 3 \times 4 = 24$. The common logarithms are designated by the symbol log_{10} or simply as log, while the natural logarithms are written as log_e or ln.

It often happens that one has access only to a table of common logarithms. To convert from one system to another, particularly from the natural to the common logarithm, the following formula is used:

$$\ln a = 2.303 \log a \qquad (9)$$

Equation (9) may be derived as follows. Let

$$\log a = x \qquad (10)$$

so that

$$a = 10^x \qquad (11)$$

and taking the natural logarithm, equation (11) becomes

$$\ln a = \ln 10^x = x \ln 10 \qquad (12)$$

Now $\ln 10 = 2.303$ and equation (12) becomes

$$\ln a = 2.303 \, x \qquad (13)$$

and substituting the identity $x = \log a$ from equation (10) into equation (13) gives the desired formula.

The application of logarithms is best demonstrated by considering several examples. In the expression,

$$\log 60.0 = 1.778$$

the digit 1 to the left of the decimal point in the logarithm is known as the *characteristic* and signifies that the number 60.0 belongs to that class of numbers with a magnitude of 10^1, and thus contains two figures to the left of the decimal point. The quantity 0.778 of the logarithm is known as the *mantissa* and is found in the table of common logarithms. It is often convenient to express the number 60.0 by writing it with one significant figure to the left of the decimal point 6.00 multiplied by 10 raised to the first power, *viz.* 6.00×10^1. The exponent of 10 then gives the characteristic and the value in the logarithm table gives the mantissa directly.

This method may be used to obtain the logarithm of 6000 as follows. The number is first written as 6.000×10^3 if it is accurate to four significant figures. The characteristic is observed to be 3, and the mantissa is found in the table as 0.7782. Hence,

$$\log 6000 = 3.7782$$

For decimal fractions which frequently appear in problems involving molar concentration the following method is used. Suppose one desires to know the logarithm of 0.0600. The number is first written as 6.00×10^{-2}. The characteristic of a number may be posi-

tive or negative; the mantissa is always positive. The characteristic in this case is -2 and the mantissa is 0.778. Hence,

$$\log 0.0600 = -2 + 0.778 = -1.222$$

Finding the number when the logarithm is given, *i.e.*, obtaining the antilogarithm, is shown by the following example. What is the value of a if $\log a = 1.7404$? The characteristic is 1 and the mantissa is 0.7404. From the table of logarithms one finds that the number corresponding to a mantissa of 0.7404 is 5.50. The characteristic is 1, so that the antilogarithm is 5.50×10^1 or 55.0.

Let us find the antilogarithm of a negative number, -2.699. Recalling that the mantissa must always be positive, we first separate the logarithm into a negative characteristic and positive mantissa:

$$-2.699 = -3.00 + 0.301$$

This transformation is easily seen in Figure 1-1 where -2.699 corresponds to going down the scale in a negative direction to -3 and coming back up the scale 0.301 units in the positive direction. Actually by this process we are subtracting 1 from the characteristic and adding 1 to the mantissa, or to the quantity

$$-2.699 = (-2) + (-0.699)$$

we subtract and add 1 to yield

$$(-2 - 1) + (-0.699 + 1) = -3 + 0.301$$

The result $(-3 + 0.301)$ is sometimes abbreviated to $(\bar{3}.301)$ where the minus sign above the 3 applies only to the characteristic. $\bar{3}$ is commonly referred to as "bar
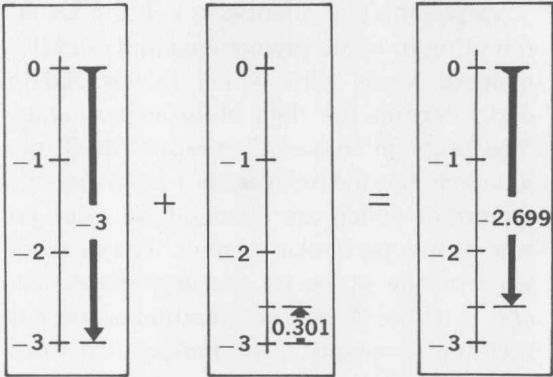

Fig. 1-1. Schematic representation for finding the antilogarithm of a negative number.

three." It is common practice in some fields, such as quantitative analysis, to use the form in which 10 is added and subtracted to give

$$\bar{3}.301 = 7.301 - 10$$

For physical chemical calculations and for plotting logarithms of numbers it is more convenient to use the form -2.699 than one of the forms having a mixture of negative and positive parts. However for use with logarithm tables the mixed form is needed. Thus in order to obtain the antilogarithm, we write the logarithm as $\bar{3}.301$. The number corresponding to the mantissa is found in the logarithm table to be 2.00. The characteristic is observed to be -3, and the final result is therefore 2.00×10^{-3}.

As seen in the table of exponents (Table 1-3), numbers may be multiplied and divided by adding and subtracting exponents. Since logarithms are exponents they follow the same rules. Some of the properties of logarithms are exemplified by the identities collected in Table 1-4.

TABLE 1-4. Rules of Logarithms

$\log ab = \log a + \log b$	$\log \dfrac{1}{a} = \log 1 - \log a = -\log a$
$\log \dfrac{a}{b} = \log a - \log b$	$\log a^2 = \log a + \log a = 2 \log a$
$\log 1 = 0$ since $10^0 = 1$	$\log \sqrt{a} = \log a^{1/2} = \tfrac{1}{2} \log a$
$\log a^{-2} = -2 \log a = 2 \log \dfrac{1}{a}$	

Variation. The scientist is continually attempting to relate phenomena and establish generalizations with which to consolidate and interpret the data of his experiments. The problem frequently resolves itself into a search for the relationship between two quantities which are changing at a certain rate or in a particular manner. The dependence of one property, the *dependent variable y*, on the change or alteration of another measurable quantity, the *independent variable x*, is expressed mathematically as

$$y \propto x \qquad (14)$$

which is read: "*y* varies directly as *x*," or "*y* is directly proportional to *x*." A proportionality is changed to an equation as follows. If *y* is proportional to *x* in general, then all pairs of specific values of *y* and *x*, say y_1 and x_1, y_2 and x_2, . . . , are proportional. Thus

$$\frac{y_1}{x_1} = \frac{y_2}{x_2} = \ldots \qquad (15)$$

Since the ratio of any *y* to its corresponding *x* is equal to any other ratio of *y* and *x*, the ratios are constant, or, in general

$$\frac{y}{x} = \text{constant} \qquad (16)$$

Hence it is a simple matter to change a proportionality to an equality by introducing a *proportionality constant, k*. To summarize, if

$$y \propto x$$

then

$$y = k x \qquad (17)$$

It is frequently desirable to show the relationship between *x* and *y* by the use of the more general notation,

$$y = f(x) \qquad (18)$$

which is read: "*y* is some function of *x*." That is, *y* may be equal to $2x$, to $27x^2$, or to $0.0051 + \log\frac{a}{x}$. The functional notation, equation (18), merely signifies that *y* and *x* are related in some way without specifying the actual equation by which they are connected. Some well-known formulas illustrating the principle of variation are shown in Table 1-5.

Graphical Methods. Scientists are not usually so fortunate as to begin each problem with an equation at hand relating the variables under study. Instead, the investigator must collect raw data and put them in the form of a table or graph where he can better observe the relationships. Constructing a graph with the data plotted in a manner so as to form a smooth curve often permits the investigator to observe the relationship more clearly, and perhaps allows him to express the connection in the form of a mathematical equation. The procedure of obtaining an empirical equation from a plot of the data is known as *curve fitting*, and is treated in books on statistics and graphical analysis as found in the Appendix, p. 606.

The magnitude of the independent variable is customarily measured along the horizontal coordinate scale called the *x* axis. The

TABLE 1-5. Formulas Illustrating the Principle of Variation

Measurement	Equation	Dependent Variable	Independent Variable	Proportionality Constant
Circumference of a circle	$C = \pi D$	Circumference, C	Diameter, D	$\pi = 3.1416 \ldots$
Density	$M = \rho V$	Mass, M	Volume, V	Density, ρ
Distance of falling body	$s = \frac{1}{2}gt^2$	Distance, s	Time, t^2	Gravity constant, $\frac{1}{2}g$
Freezing point depression	$\Delta T_f = K_f m$	Freezing point depression, ΔT_f	Molality, m	Cryoscopic constant, K_f

dependent variable is measured along the vertical scale or the y axis. The data are plotted on the graph and a smooth line is drawn through the points. The x value of each point is known as the x coordinate or the *abscissa;* the y value is known as the y coordinate or the *ordinate.* The intersection of the x axis and the y axis is referred to as the *origin.* The x and y values may be either negative or positive.

The simplest relationship between two variables, where the variables contain no exponents other than one (*first degree equation*), yields a straight line when plotted on rectangular graph paper. The straight-line or linear relationship is expressed as

$$y = ax + b \qquad (19)$$

in which y is the dependent variable, x is the independent variable, and a and b are constants. The constant a is the *slope* of the line; the greater the value of a the steeper the slope. It is expressed as the change in y with the change in x or $a = \dfrac{\Delta y}{\Delta x}$; a is also the tangent of the angle that the line makes with the x axis. The slope may be positive or negative depending on whether the line slants upward or downward to the right. When $a = 1$ the line makes an angle of $45°$ with the x axis ($\tan 45° = 1$) and the equation of the line may then be written,

$$y = x + b. \qquad (20)$$

When $a = 0$ the line is horizontal, *i.e.,* parallel to the x axis, and the equation reduces to

$$y = b. \qquad (21)$$

The constant b is known as the y *intercept* and signifies the point at which the line crosses the y axis. If b is positive, the line crosses the y axis above the x axis; if negative, it intersects the y axis below the x axis. When b is zero the equation may be written,

$$y = ax \qquad (22)$$

and the line passes through the origin.

TABLE 1-6. Refractive Indices of Mixtures of Benzene and Carbon Tetrachloride

(x) Conc. CCl_4 Volume Per Cent	(y) Refractive Index (n)
10.0	1.497
25.0	1.491
33.0	1.488
50.0	1.481
60.0	1.477

The results of the determination of the refractive index of a benzene solution containing increasing concentrations of carbon tetrachloride are found in Table 1-6. The data are plotted in Figure 1-2 and are seen to produce a straight line with a negative slope. The equation of the line is obtained by using the two-point form of the linear equation,

$$y - y_1 = \frac{y_2 - y_1}{x_2 - x_1}(x - x_1) \qquad (23)$$

The method involves selecting two widely separated points (x_1, y_1) and (x_2, y_2) on the line and substituting into the two-point equation.
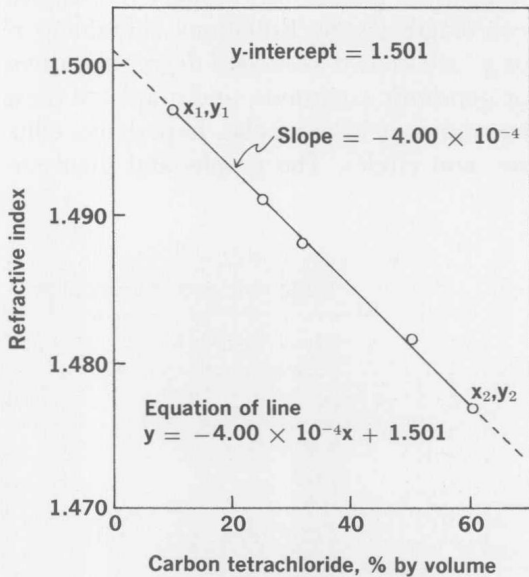

FIG. 1-2. Refractive index of the system benzene-carbon tetrachloride.