Fitzpatrick's Dermatology in General Medicine, 7th Edition

Content

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3. Dedication

This Seventh Edition of *Fitzpatrick's Dermatology in General Medicine* is dedicated to the memory of two innovators in the field, whose visionary approach to dermatology is reflected throughout:

Thomas B. Fitzpatrick, MD, PhD and Irwin M. Freedberg, MD

Dr. Fitzpatrick (d. 2003) was Wigglesworth Professor of Dermatology Emeritus at Harvard Medical School, and the Founder of DIGM as well as its Editor-in-Chief for the first four editions.

Dr. Freedberg (d. 2006) was the George Miller MacKee Professor of Dermatology, New York University Medical Center, and the Editor-in-Chief for the fifth and sixth editions and led the book to new heights.

4. Preface

We are proud to present this Seventh Edition of *Fitzpatrick's Dermatology in General Medicine* (DIGM), which has been reorganized and substantially rewritten to reflect the current state of the science, practice, and art of dermatology. More than 50 percent of the text and figures of our 257 chapters are new to this edition, as are 50 percent of the authors. Integration of the basic and clinical science remains the DIGM signature, and the organization of the book is intended to promote understanding of the skin as an adaptive organ that changes throughout the life span. Clinical disease chapters are now grouped within sections by pathogenic and causative mechanism, and each section is introduced by the relevant basic science chapters.

To achieve the goal of making the text truly encyclopedic and readily accessible to readers at all levels of expertise, there are now two versions of the book, a concise printed version and an on-line version. Throughout the text, when additional on-line content is available, the following icon is present in the text to alert the reader:  To save space in print, the majority of references are available on-line only. The on-line edition and the on-line references can be found at www.digm7.com. Without sacrificing its focus on the skin as integral to and reflective of overall health, the new edition provides increased emphasis on therapy, dermatologic surgery, and cosmetic dermatology. The on-line edition provides additional detailed text for full and exhaustive coverage of each subject, many additional images, charts, and algorithms, and comprehensive up-to-date literature references.

The layout of DIGM has also changed. Readers will now find an “At a Glance” overview at the beginning of each chapter; algorithms for diagnosis and therapy to expedite decision making; boxes on differential diagnosis; and a wealth of diagrams, charts, and additional new images to enhance understanding of the text. Many more additional images can be found in the electronic version.

The new features and improved aspects of DIGM showcase the wealth of the contributing authors' knowledge. We have endeavored to integrate that knowledge into a single comprehensive and consistent reference that will serve the educational and reference needs of the entire dermatology community. We hope that you will find this goal achieved and use DIGM for this purpose for many years to come.

Klaus Wolff

Lowell A. Goldsmith

Stephen I. Katz

Barbara A. Gilchrest

Amy S. Paller

David J. Leffell

5. Acknowledgments

We are very grateful to the contributing authors who worked closely with us and one another under great time constraints to maintain the excellent standards of DIGM in a radically new format. We are also indebted to our families for their understanding and support, as well as the time with us they gave up during the development of the new edition. Support staff at our institutions who helped us with this edition—Renate Kosma, Jacy Bernal, and Grace Camire—deserve special recognition for their extraordinary level of assistance with manuscripts throughout the process of review and publication. The vibrancy of the new diagrams, algorithms, and charts is the work of Susan Gilbert, CMI, to whom we are grateful for her diligent efforts done within a very difficult schedule. Finally, we wish to acknowledge the excellent guidance and hard work of the McGraw-Hill team, especially Anne M. Sydor, Robert Pancotti, Sherri Souffrance, Charissa Baker, Armen Ovsepyan, Kevin Moran, Helen Parr, and Alexa Blondell.

Klaus Wolff

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Barbara A. Gilchrest

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6. Part 1 - Introduction

6.1 Section 1 - General Considerations

6.1.1 Chapter 1 - The Epidemiology and Burden of Skin Disease

Chapter 1

The Epidemiology and Burden of Skin Disease

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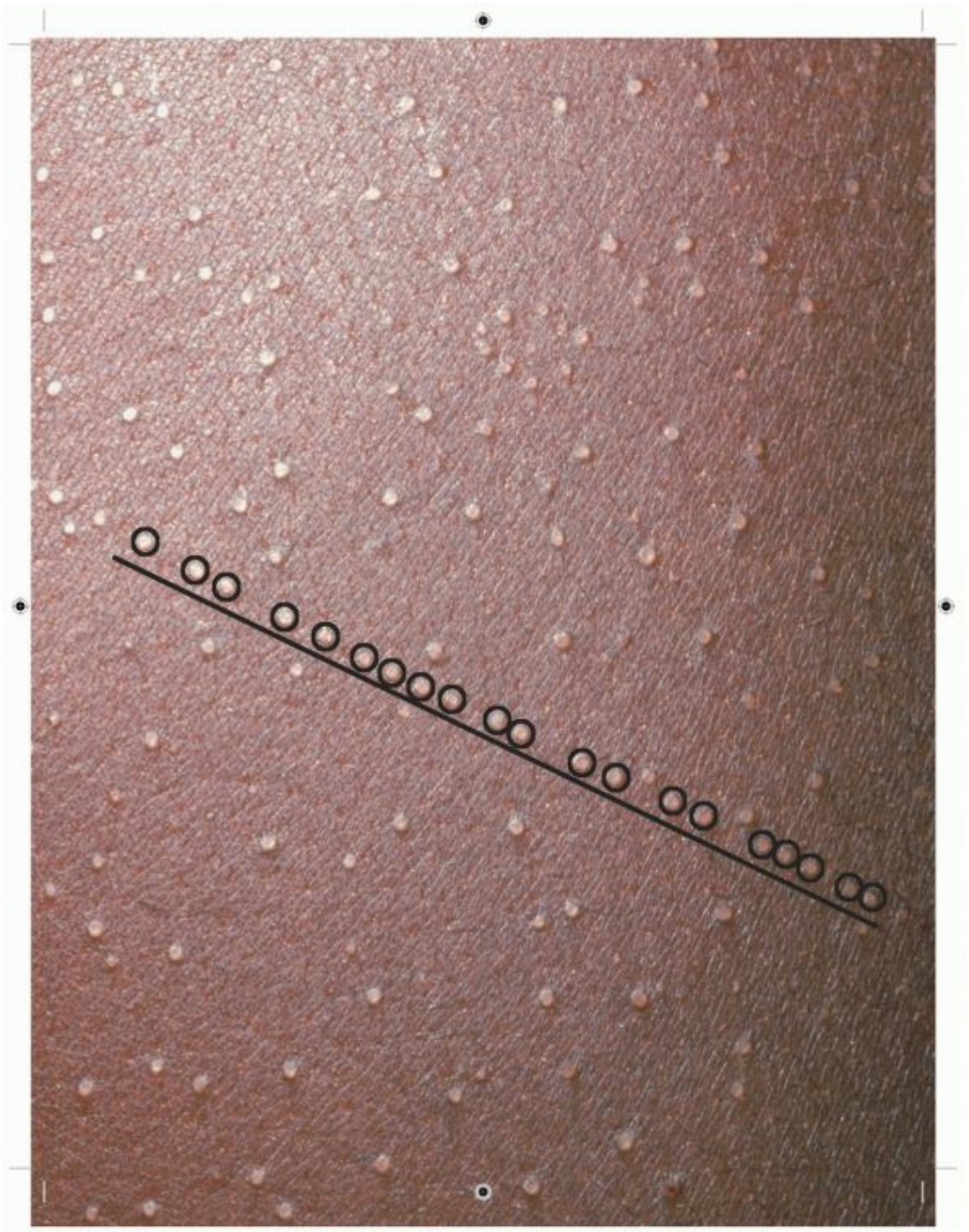

Linear lesion. (Illustration by Glen Hintz, MS. Dermatology Lexicon Project. NIH-NIAMS Contract No. N01-AR-1-2255.)

Scientists in health-related fields focus on phenomena at different levels. For laboratory scientists, the focus is at the molecular, cellular, or organ system level;

for clinical scientists, the focus is on the patient; and for public health practitioners, the focus is on the population. Epidemiology is the basic science of public health.

Epidemiology has many subdivisions and offshoots. Often the *epidemiology of a disease* in a clinical review refers primarily to its frequency and distribution in the population and estimates of its morbidity and mortality. These data are derived by descriptive epidemiology. Case-control, cohort, and cross-sectional studies may seek to identify risk factors and causes of disease and form the core of analytical epidemiology. Evaluations of public health interventions (experimental epidemiology) constitute the third major branch of classic epidemiology. The basic principles of epidemiology have found broad application in many areas, including understanding the public health implications of naturally occurring and synthetic compounds (molecular epidemiology), the complex interactions of genetic and environmental factors in disease (genetic epidemiology), the formulation of better diagnostic and treatment strategies for patients based on available evidence (clinical epidemiology), and the structuring of health care delivery for better outcomes and greater efficiency (health services research). The reader is referred to other sources for a more detailed discussion of various topics in dermatoepidemiology.[1], [2], [3]

▪ TYPES OF EPIDEMIOLOGIC STUDIES

Three of the many types of epidemiologic studies are mentioned here because of their prominence in epidemiologic research. The randomized, controlled trial is a particularly rigorous type of study appropriate to the evaluation of public health interventions. In general, the intervention is performed on a random sample of the study population, and the entire study population is then observed for the occurrence of the outcome in question. The random assignment of intervention allows the more rigorous application of many statistical techniques and reduces the potential for bias. Elimination of biases permits these studies to evaluate the efficacy and impact of an intervention more accurately than trials that do not assign the intervention randomly. Standards for reporting have been published[4] (http://www.consort-statement.org; last accessed June 29, 2006) and adopted by leading dermatology journals to improve assessment of their validity and their use in subsequent systematic reviews[5] (see Chap. 2).

When evaluating risk factors for disease, it is frequently impossible to assign the risk factor randomly. Hence, inference is based on observational studies. In classical cohort studies, a group with exposure to the risk factor and a group without are chosen and observed over time. Occurrences of the study outcome are counted and compared between groups. Although more vulnerable to bias than randomized trials,

cohort studies, in which exposure to the risk factor is known well before the study outcome is knowable, avoid potentially serious biases. In a cohort study, the incidence of the study outcome can be measured directly in each group, and the relative risk can be measured directly as the ratio of the incidence between the two groups.

Cohort studies often are quite expensive to conduct because they require following a large population over time and may be impossible if the outcome being studied is uncommon. Hence, observational studies often use the case-control approach, in which cases with the outcome being studied and appropriate controls are investigated to determine their past exposure to the risk factor. Relative risks generally can be estimated by this approach, although incidence of the disorder cannot. Readers are referred to standard texts for more detail regarding epidemiologic study designs.[6] Case-control and cohort study methods in dermatology also have been reviewed.[7-9]

▪ BIAS AND CONFOUNDING

The problem with inference from observational studies is that one may be led to draw erroneous conclusions. In particular, an association that is found between an exposure and a disease may be an artifact due to one or more of the many forms of bias or confounding. Proper inference regarding cause and effect requires understanding these possible artifacts and their potential impacts.[10]

Selection bias occurs when factors that lead to selection of the study population affect the likelihood of the outcomes or exposures evaluated. For example, a case-control study of cutaneous lymphoma may recruit its cases from sources that typically include a high proportion of referred patients. If controls are recruited from a local clinic population, their socioeconomic

status and location of residence may be substantially different from those of the cases simply due to the method of recruitment. Under these circumstances, an association of cutaneous lymphoma with occupation may be noted. It then becomes important to note that the observed association may be due not to a carcinogenic chemical in the workplace but rather to the method by which cases and controls were selected. Similarly, if one were conducting a cohort study of the effect of breast-feeding on the risk of atopic dermatitis, it would be important to select breast-fed and bottle-fed infants from similar environments.

Information bias occurs when the assessment of exposure or outcome may differ between the groups being compared. People who were exposed to a publicized environmental toxin may be more likely to seek care for minor symptoms or signs (and hence be more likely to be diagnosed and treated) than those who were not so exposed, even if the exposure had no biologic effect. Similarly, people who are diagnosed with a disease may be more likely to recall past exposures than healthy controls.

Confounding occurs when an observed association (or lack thereof) between exposure and disease is due to the influence of a third factor on both the exposure and the disease. For example, people who use sunscreens may have more intense sun exposure than those who do not, and intense sun exposure is one cause of melanoma. Hence, observational studies may mistakenly conclude that sunscreen use is a cause of melanoma when the observed association is due to sunscreen use serving as an indicator of a lifestyle involving intense sun exposure.

▪ CAUSAL INFERENCE

Key issues in the public health arena often must rely on observational data for inferring cause and effect; in these situations, the validity and generalizability of the individual studies and of the totality of the evidence must be carefully examined. The following criteria generally are applied for causal inference when an association is found. Although they are described for inferring causality between an exposure and a disease, they are more generally applicable to epidemiologic causal inference.

Time Sequence

The exposure must precede the disease. This concept is simple and obvious in the abstract but sometimes difficult to establish in practice because the onset of disease may precede the diagnosis of disease by years, and the timing of exposure is often not well defined.

Consistency on Replication

Replication of the observed association is key and provides the strongest evidence if the replications are many and diverse and with consistent results. The diversity of the replications refers to varied contexts as well as to study designs with different potential weaknesses and strengths.

Strength of Association

True causal relationships may be strong (i.e., high relative risk) or weak, but artifactual associations are unlikely to have a high relative risk. If the association between factors *x* and *y* is due to the association of both with confounding variable *z*, the magnitude of the association between *x* and *y* always will be less than the magnitude of the association of either with *z*.

Graded Association

Also described as *biologic gradient*, this criterion refers to an association of the degree of exposure with occurrence of disease, in addition to an overall association of presence of exposure with disease. This dose-response relation may take many forms, as degree of exposure may, for example, refer to intensity, duration, frequency, or latency of exposure.

Coherence

Coherence refers to plausibility based on evidence other than the existence of an association between this exposure and this disease in epidemiologic studies. Coherence with existing epidemiologic knowledge of the disease in question (e.g., other risk factors for the disease and population trends in its occurrence) and other disorders (including but not limited to related disorders) supports inference. Coherence with existing knowledge from other fields, particularly those relevant to pathogenesis, is critically important when those fields are well developed. It may involve direct links, which are preferred, or analogy. Just as observations in the laboratory assume greater significance when their relevance is supported by epidemiologic data, the reverse is equally true.

Experiment

Experimental support is critical when feasible. As noted in Types of Epidemiologic Studies, the strongest inferences derive from results of randomized trials, although other experimental designs and quasi-experimental designs may contribute useful evidence.

More detailed discussions of these issues are available.[11,12]

▪ INVESTIGATION OF DISEASE OUTBREAKS

Although outbreaks of disease vary tremendously, use of a standard framework for investigation is important to address the public health issues efficiently (see Chap. 3). The Centers for Disease Control and Prevention has outlined this framework as a series of 10 steps, which are described in more detail at http://www.cdc.gov.

- *Preparation.* Before initiating fieldwork, background information on the disease must be gathered, and appropriate interinstitutional and interpersonal contacts should be made.
- *Confirm the outbreak.* Publicity, population changes, or other circumstances may lead to an inaccurate perception that more cases than expected have occurred. Hence, local or regional data should be sought to confirm the existence of an increased frequency of disease.
- *Confirm the diagnosis.* Symptoms and signs of persons affected should be determined and laboratory findings confirmed, perhaps with the assistance of reference laboratories.
- *Establish a case definition, and find cases.* Careful epidemiologic investigation will involve precise and simple case definitions that can be applied in the field. Efforts to find and count additional cases beyond those reported initially is key to defining the scope of the outbreak.
- *Establish the descriptive epidemiology.* The cases can now be characterized in terms of *time,* including development of an epidemic curve that describes the changes in magnitude of the outbreak; *place,* including mapping the distribution of cases; and *person,* the demographic and potential exposure characteristics of cases.
- *Develop hypotheses.* On the basis of the data gathered in steps 1 through 5 and the input of other individuals, plausible hypotheses about causality can be developed for further evaluation.

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- *Conduct analytical epidemiologic investigations.* If the data gathered do not yet clearly prove a hypothesis, cohort and case-control investigations can be conducted to verify or disprove the hypotheses.
- *Revise hypotheses and obtain additional evidence as needed.* Steps 6 and 7 are repeated, each building on prior iterations, to establish the causal chain of events.
- *Implement control measures.* As soon as the causal chain of events is understood, prevention and control measures are initiated.
- *Communicate results.* An outbreak investigation is not complete until the results have been appropriately communicated to the relevant communities.

▪ DESCRIPTIONS OF DISEASE IN POPULATIONS: MEASURES OF DISEASE BURDEN

No single number can completely describe the burden of skin disease because that burden has many dimensions and because the term *skin disease* itself is rather ambiguous. Many disorders with substantial morbidity or mortality, such as melanoma or lupus erythematosus, affect multiple organ systems. The degree of skin involvement may vary widely from patient to patient and within the same patient from time to time. Diseases not typically treated by dermatologists, such as thermal burns, often are excluded from estimates of the burden of skin disease even though they primarily involve the skin. In addition, some diseases treated most often by dermatologists may be classified in a different category by funding agencies or others [e.g., melanoma is classified as an oncologic disorder as opposed to a disease of the skin by the National Institutes of Health and by the *International Classification of Diseases,* (http://www.who.int/classifications/apps/icd/icd10online/, accessed June 29, 2006) even though it almost always arises in the skin]. Organ systems are interrelated, and the overlap is sufficiently great that any definition of skin disease is necessarily arbitrary, and any global estimate of the public health burden of these diseases is therefore open to challenge. Typical measures of disease burden are discussed in the following sections.

Mortality

Mortality is a critical measure of disease impact. Death certification is universal in the United States, and the *International Classification of Diseases* code of the underlying cause of each death is recorded. For the year 2002, there were 14,968 deaths reported as due to “skin disease” in the United States, of which most were due to melanoma (Table 1-1). Additional major causes included other skin cancers (primarily keratinocyte carcinomas), infections of the skin, and skin ulcers (primarily decubitus ulcers). Bullous disorders represented about 1 percent of these deaths. The total number of skin disease deaths, of course, depends critically on the definition of skin disease, as noted in Descriptions of Disease in Populations: Measures of Disease Burden.

TABLE 1-1 Skin Disease Deaths, United States, 2002

DISEASE	DEATHS (N)
Cancers	11,031
Melanoma	7514
Genital	1017
Lymphoma	109
Other cancers	2391[a] (primarily basal and squamous cell carcinoma)
Ulcers	1671
Bacterial infections	1283
Bullous disorders	164
Other causes	819
Total	14,968

[a] We estimate that approximately one-half of these are misclassified squamous cell carcinomas arising from mucosal surfaces in the head and neck.[16] Adapted from http://wonder.cdc.gov/mortlCD10J. html (verified

June 13, 2006).

In addition to the total number of deaths, mortality typically is expressed as an age-adjusted rate to facilitate comparisons among populations with different age distributions. Statements of age-adjusted rates of mortality (or other results standardized by age) should be accompanied by an indication of the standard used in the adjustment to avoid potentially misleading inferences. For example, when 1998 melanoma mortality rates are estimated using the 2000 U.S. population standard, the result is 50 percent higher than if the 1940 U.S. standard population is used (1.8 vs. 1.2 per 100,000 per year for women and 4.1 vs. 2.7 per 100,000 per year for men). Similarly, when years of potential life lost is reported, the reader must be wary of different definitions that may be applied. In one analysis, a decline in mortality from melanoma was noted by one definition that was not observed with another.[13]

Careful analyses of mortality include assessment of the validity of the data. Melanoma mortality statistics appear to be reasonably accurate.[14,15] However, deaths from keratinocyte carcinomas are overestimated by a factor of 2 (mostly due to the erroneous inclusion of mucosal squamous cell carcinomas of the head and neck region),[16,17] and deaths from cutaneous lymphoma are underestimated by about 40 percent.[15]

Incidence

Incidence refers to the number of new cases of a disorder. Mortality is low for most skin diseases; hence, incidence may be a more useful measure for the assessment of burden of skin disease. However, many features of skin diseases make their incidence difficult to measure. For example, for many skin disorders, there are no diagnostic laboratory tests, and, in fact, some disorders may evade physician diagnosis (e.g., allergic reactions). Incidence for reportable communicable diseases

in the United States is published periodically based on reports to health departments, although under-reporting of skin diseases due to failure to present for medical care or to misdiagnosis is a concern (Table 1-2). Incidences of melanoma and cutaneous lymphoma have been published based on data from a system of nationwide cancer registries, yet under-reporting remains a potential concern with these data.[18,19] Special surveys have been conducted to estimate incidence of other disorders, such as keratinocyte carcinomas, although a system of sentinel registries would be required for nationwide assessment.[20] For some diseases unlikely to evade medical detection due to their severity, such as toxic epidermal necrolysis, efforts to estimate incidence have met with considerable success.[21,22] Specific contexts that permit more accurate incidence estimates include the workplace; for example, where occupational skin disease is a prevalent problem.[23]

Cohort Patterns

Cohort patterns of changes in mortality or incidence typically are observed when exposures determined in childhood predict frequency of disease throughout the life span. A classic example is melanoma mortality, for which sun exposure in childhood is an important determinant. A birth cohort is defined as the group of individuals born

within a defined (e.g., 10-year) period. Melanoma mortality generally increases as a power function of age within a birth cohort. Until recent decades, each successive birth cohort had higher risk than its predecessor; hence, the curves of mortality versus age were shifted upward. Thus the cross-sectional relationship of mortality versus age and the increase in mortality risk during most of the twentieth century followed a cohort pattern. For many countries in the past several decades a decline in melanoma mortality has been observed in younger age groups despite an increase in older age groups, suggesting a lower baseline in these mortality-versus-age curves for recent cohorts and hence a likely future decline in overall melanoma mortality.

TABLE 1-2 New Cases of Selected Reportable Diseases in the United States

	1940	1950	1960	1970	1980	1990	2000	2005
Acquired immunodeficiency syndrome	—	—	—	—	—	41,595	40,758	30,568
Anthrax	76	49	23	2	1	0	1	—
Congenital rubella	—	—	—	77	50	11	9	1
Congenital syphilis	—	—	—	—	—	3865	529	273
Diphtheria	15,536	5796	918	435	3	4	1	—
Gonorrhea	175,841	286,746	258,933	600,072	1,004,029	690,169	358,995	314,370
Hansen	—	44	54	129	223	198	91	89

disease								
Lyme disease	—	—	—	—	—	—	17,730	21,304
Measles	291,162	319,124	441,703	47,351	13,506	27,786	86	62[a]
Plague	1	3	2	13	18	2	6	7
Rocky Mountain spotted fever	457	464	204	380	1163	651	495	1843
Syphilis (primary and secondary)	—	23,939	16,145	21,982	27,204	50,223	5979	8020
Toxic shock syndrome	—	—	—	—	—	322	135	96
Tubercu	102	121	55,	37,	27,7	25,	16,	11,

losis[b]	,984[c]	,742[c]	494	137	49	701	377	547
U.S. population (millions)	132	151	179	203	227	249	281	296

— = data not available.

[a] Fifty-one indigenous cases.

[b] Reporting criteria changed in 1975.

[c] Data include newly reported active and inactive cases.

Adapted with permission from Weinstock MA, Boyle MM: Statistics of interest to the dermatologist, in *The Year Book of Dermatology and Dermatologic Surgery, 2006,* edited by Thiers BH, Lang PG Jr. Philadelphia, Elsevier Mosby, 2006, p 30.

Prevalence

Prevalence refers to the proportion of the population affected by a disorder. Because many skin diseases are nonlethal yet chronic, prevalence is a particularly important measure of frequency in dermatology. Population-based data on prevalence of skin disease for the United States were obtained in the first Health and Nutrition Examination Survey, which was conducted in the early 1970s.[24] Despite its limitations, this study was notable because the sample was representative of the general U.S. population, the number surveyed was large (over 20,000), and the entire surveyed population was examined by physicians (primarily dermatology residents), so the resulting estimates were not dependent on patients' ability or

inclination to seek medical care. Indeed, one of the findings of the survey was that nearly one-third of those examined had one or more skin conditions judged to be significant enough to merit a visit to a physician. The most common conditions and their age- and genderspecific prevalences are indicated in Table 1-3 and Fig. 1-1. A similar survey in the United Kingdom of over 2000 Londoners in 1975 noted that almost one-quarter of adults had a skin condition serious enough to warrant medical care.[25] Other efforts have focused on obtaining prevalence estimates of specific conditions with special surveys.[26,27]

Lifetime Risk

Lifetime risks for certain disorders are quoted commonly, although their validity can be questioned. Lifetime risk can be measured only in retrospect, and even then it reflects competing causes of mortality in addition to incidence. It is commonly quoted for disorders such as cutaneous malignancies that are changing substantially in incidence, yet those changes are frequently ignored in its calculation, and, in any case, projections of future changes are quite speculative and may be misleading.[28]

Number of Physician Visits

Number of physician visits for a condition is one practical measure of its frequency that may reflect its incidence, prevalence, and severity, as well as access to health care. Table 1-4 lists frequencies of dermatologist and other physician outpatient visits for some of the most common skin conditions. A

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feature of this measure of disease frequency is its direct relation to expenditures for care of the disease.

TABLE 1-3 Prevalence of Skin Conditions—United States, 1971-1974[a]

	MALE	FEMALE	BOTH SEXES
• Dermatophytosis	131	34	81
• Acne (vulgaris and cystic)	74	66	70
• Seborrheic dermatitis	30	26	28
• Atopic dermatitis/eczema	20	18	19
• Verruca vulgaris	9	6	8
• Malignant tumors	6	5	6
• Psoriasis	6	5	6
• Vitiligo	6	4	5
• Herpes simplex	4	5	4

[a]Cases per 1000 population.

From Skin conditions and related need for medical care among persons 1-74 years, United States, 1971-1974. *Vital Health Stat* [11], no 212, U.S. Department of Health, Education, and Welfare, November 1978.

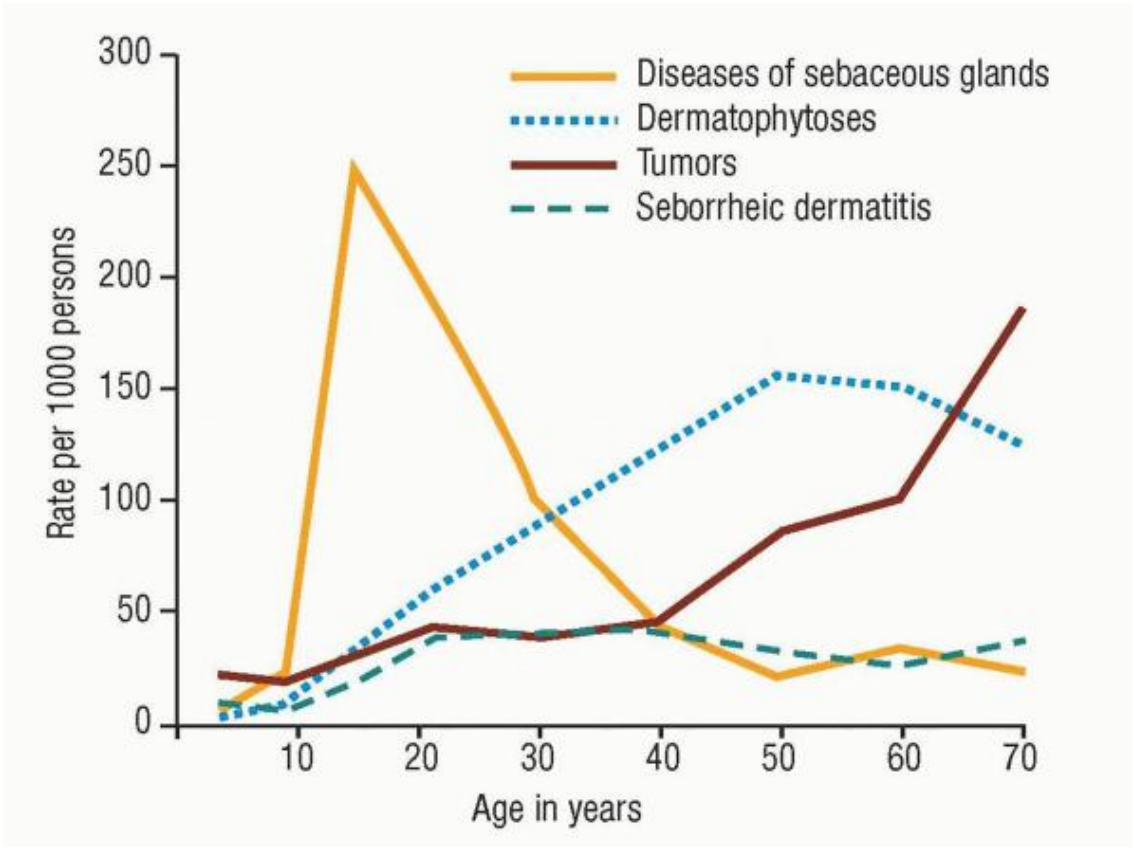

FIGURE 1-1 Prevalence rates for the four leading types of significant skin pathology among persons 1 to 74 years, by age, in the United States, 1971-1974.

Other Measures of Morbidity: Conceptual Issues

The consequences of skin disease for a population may be difficult to determine comprehensively because these conditions most often do not affect survival.[29] Furthermore, the most important gauges of skin disease status and progression (i.e., the physical examination and patients' reports) are difficult to measure and compile. For example, a patient with psoriasis may have thickening and scaling of the palms (a bodily impairment), which affects his or her functioning (e.g., use of the hands), activities (role at work), and quality of life. Moreover, the challenges in measuring these complex constructs are further compounded because people understand and value these aspects of health very differently because of age, gender, cultural conceptions, or access to health care. In fact, the measurement of nonfatal consequences of disease is the subject of much international scientific and political attention (http://www3.who.int/icf/icftemplate. cfm, accessed July 3, 2006).

TABLE 1-4 Visits to Non-Federal Office-Based Physicians in the United States, 2003[a]

	TYPE OF PHYSICIAN		
DIAGNOSIS	DERMATOLOGIST[b]	OTHER	ALL PHYSICIANS
Acne Vulgaris	3772 (12.7%)	[c]	4402 (0.5%)
Eczematous dermatitis	2452 (8.2%)	5676 (0.7%)	8128 (0.9%)
Warts	1400 (4.7%)	1567 (0.2%)	2967 (0.3%)
Skin cancer	2103 (7.1%)	1459 (0.2%)	3562 (0.4%)
Psoriasis	1100 (3.7%)	[c]	1268 (0.1%)
Fungal infections	[c]	2104 (0.2%)	2555 (0.3%)
Hair disorders	772 (2.6%)	[c]	1690 (0.2%)
Actinic keratosis	2653 (8.9%)	[c]	3031 (0.3%)

Benign neoplasm of the skin	2791 (9.4%)	[c]	3935 (0.4%)
All disorders	29,801 (100%)	876,222 (100%)	906,023 (100%)

[a]Estimates in thousands.

[b] Percentage of total visits is in parentheses.

[c] Figure does not meet standard of precision.

Adapted with permission from Weinstock MA, Boyle MM: Statistics of interest to the dermatologist, in *The Year Book of Dermatology and Dermatologic Surgery, 2006,* edited by Thiers BH, Lang PG Jr. Philadelphia, Elsevier Mosby, 2006, p 39.

A crucial point for skin diseases is that a patient's experiences of effects of skin disease on his or her activities and well-being are important for determining the overall consequences of that disease. These experiences may not be assessed with global measures that focus on single aspects of health. For example, skin diseases that are visible and affect appearance may result in social stigma and mood changes, which would not be measured with metrics that are based on dysfunction.[30]

Other Measures of Morbidity: Issues in Quantification

Like all assays, measures of the nonfatal consequences of diseases must have certain characteristics of accuracy.[31] For example, they must be *reliable* in that the variability in results among subjects who truly differ should be greater than the variability when a stable subject is examined repeatedly. The measures must have evidence of *validity,* which refers to the extent to which an instrument measures what it is supposed to measure and does not measure something else. Finally, health outcome measures also must demonstrate *responsiveness,* the ability to detect

clinical change. In general, the accuracy of measures of disease status and morbidity in dermatology has not been evaluated adequately.[32] Furthermore, even when a validated instrument exists, the clinical significance of scores or changes in scores often cannot be judged until the tool is used widely and scores are available for many patients with disease of varying severity. Finally, a significant challenge is developing a consensus among dermatologists about the specific clinical features of an individual disease that are important to include in such measures. For example, criteria for clinically important improvement have been developed for some rheumatologic conditions[33] that, like skin diseases, are chronic and are best assessed using clinical rather than laboratory criteria.

Impairment

The extent to which a specific skin disease disrupts the skin itself is related both to the percentage of body surface area involved and to physical signs of the eruption, such as the amount of induration and the degree of scale. Given the pleomorphism of skin eruptions and lesions, most dermatologic severity-of-disease measures are disease-specific. Among the most studied instruments to measure clinical severity of disease are the Psoriasis Area and Severity Index (PASI)[34] and the Severity Scoring of Atopic Dermatitis (SCORAD) index.[35] With the PASI, severity of disease is assessed by judgment of the degree of involvement of four body regions with signs of erythema, induration, and desquamation.

The SCORAD index combines an assessment of disease area with six clinical signs of disease intensity (scales to measure pruritus and sleep loss also can be included). These instruments share certain problems; for example, estimates of body surface area are often unreliable,[36] and investigators (and patients) may not agree that the selected clinical signs represent the important features of disease severity.[37]

Functioning and Quality of Life

Substantial progress has been made in the development and testing of patients' reports of the effects of their skin diseases on their activities and quality of life. Several generic instruments are available to measure skin-related quality of life associated with dermatologic disease of any sort.[38-41] Data continue to be accumulated about the performance of these instruments (including the use of sophisticated psychometric methods[42] and the interpretation of their scores.[43] An important conclusion from these studies is that correlations between the quality-of-

life effects of skin diseases and their clinical severity as assessed by physicians are modest at best and may in fact be quite low. This finding is also typical of many nondermatologic diseases and implies that a comprehensive assessment of patients with skin disease should include measurement of clinical severity as well as its effects on quality of life.[44]

Utilities

A utility is a numeric measure of the value a patient places on a given health state compared with other health states. In the measurement of utilities, a variety of procedures are used (such as visual analog scales and time tradeoff exercises) to assign a numerical value (or utility) to health states. This value reflects patients' preferences for the health states, in which 1.0 represents perfect health and 0.0 represents death. Utilities are advantageous because they permit the incorporation of patient preferences into medical care decisions. Also, because they describe improvements in morbidity with a single weighted metric, utilities are used for the evaluation of complex tradeoffs such as the calculation of cost-effectiveness, in which the costs of treatments are compared with the values of the health states they make possible. Utilities are controversial, however, because they can be difficult to measure and can vary widely among patients in unpredictable ways. An increasing number of studies exist that formally measure utilities of patients with skin diseases.[45]

Costs

Costs of skin disease depend on the perspective from which they are measured, because the costs to insurers and patients may be quite different from the overall cost to society. Also, because most skin diseases are chronic and are cared for in the outpatient setting, estimation of both their monetary and intangible costs is difficult. A recent study estimated the overall direct and indirect cost to payers, patients, and society of 22 skin diseases.[46] In addition, costs for individual skin conditions have been calculated, and therapies have been evaluated in relation to their benefits and effectiveness.[47,48]

▪ QUALITY OF CARE IN DERMATOLOGY

Health services research uses many of the scientific methods from epidemiology, clinical epidemiology, and the quantitative social sciences to study and improve the quality of health care. From the perspective of health services research, the processes involved in the provision of health care, as well as the particular therapeutic interventions and patient and provider characteristics, are all

potentially important determinants of the quality of care. Dermatologic health services research is still new, and much attention has focused on studies of the effectiveness of care (i.e., outcomes of health care as it is usually practiced). To inform standard care, however, efficacy of interventions is also important (i.e., the results of interventions implemented in the idealized circumstances of a randomized clinical trial). Many of the examples cited earlier demonstrate a sharpened focus in dermatology on accurate measurement of the clinical encounter. This capacity to measure the progress of chronic diseases and their care will permit rigorous efforts to evaluate and improve the quality of that care.

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6.1.2 Chapter 2 - Evidence-Based Dermatology

Chapter 2

Evidence-Based Dermatology

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▪ BRIEF HISTORY OF EVIDENCE-BASED MEDICINE

Hundreds of randomized controlled clinical trials were conducted between 1950 and the 1970s. However, their results were not catalogued or used systematically to inform medical decision making. In 1972 Archie Cochrane, a British epidemiologist and physician, published his response to being asked to evaluate the effectiveness of the British National Health Service in delivering health care to the population of the United Kingdom. In his analysis he concluded that medical science was poor at distinguishing interventions that were effective from those that were not and that physicians were not using available evidence from clinical research to inform their decision making.[6] See http://www.cochrane.org/cochrane/archieco.htm for more information on Archie Cochrane.

Groups of like-minded epidemiologists and physicians responded to Archie Cochrane's challenge by examining the methods by which medical decisions and conclusions were reached and proposed an alternative approach based on finding, appraising, and using available data from clinical research involving intact patients.[7] In 1985 Sackett et al. published *Clinical Epidemiology: A Basic Science for Clinical Medicine*, which detailed the rationale and techniques of this evidence-based approach.[7] These authors and others reduced the rules of evidence to a small subset of principles that were easier

to teach and to understand, and reintroduced the concept in 1992.[8] They named this technique *evidence-based medicine* (EBM). It was defined as the conscientious, explicit, and judicious use of the best current evidence in making decisions about

the care of individual patients.[8] Whereas making decisions about therapy has been the primary focus of EBM, its principles have been extended to diagnosis, prognosis, avoidance of the harmful effects of interventions, determination of cost effectiveness, and economic analyses.

▪ EVIDENCE-BASED MEDICINE AT A GLANCE

- Evidence-based medicine (EBM) is the use of the best current evidence in making decisions about the care of individual patients.
- EBM is predicated on asking clinical questions, finding the best evidence to answer the questions, critically appraising the evidence, applying the evidence to the treatment of specific patients, and saving the critically appraised evidence.
- The EBM approach is most appropriate for frequently encountered conditions.
- Results from well-designed clinical studies involving intact patients are at the pinnacle of the hierarchy of evidence used to practice evidence-based medicine.
- Recommendations about treatment, diagnosis, and avoidance of harm should take into account the validity, magnitude of effect, precision, and applicability of the evidence on which they are based.

The introduction of EBM was met with considerable hostility. It was perceived as cookbook medicine, old hat, too restrictive, and an insult to those already trying to practice good medical care. The definition was softened to include the integration of independent clinical expertise, best available external clinical evidence from systematic research, and the patient's values and expectations.[2]
The Cochrane Collaboration was formed to some extent in response to Archie Cochrane's challenge to generate critical summaries, organized by specialty or subspecialty and updated periodically, of all relevant randomized controlled trials.[9] Created and maintained through the collaborative efforts of volunteers, the Cochrane Library is an impressive and useful compendium of systematic reviews, abstracts of systematic reviews, and the Cochrane Central Register of Controlled Trials, a database of over 473,000 controlled clinical trials (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). The Cochrane Library is the most complete and best index database of randomized controlled clinical trials and controlled clinical trials and is the best and most efficient place to find evidence about therapy.

The acceptance of EBM in the specialty of dermatology has been slow and reluctant. The term and principles are understood by few and misunderstood by many. EBM is

perceived as an attempt to cut costs, impose rigid standards of care, and restrict dermatologists' freedom to exercise individual judgment. Practicing EBM in dermatology is hampered by the continued belief among dermatologists that clinical decisions can be guided by an understanding of the pathophysiology of disease, logic, trial and error, and nonsystematic observation.[1,10] It is hampered also by a lack of sufficient data in many areas. As with EBM in general, therapy is often primarily emphasized; however, evidence-based approaches to diagnosis and avoidance or evaluation of harm are also important considerations.

▪ WHAT IS "THE BEST EVIDENCE"?

Practicing EBM is predicated on finding and using the best evidence. Potential sources of evidence include knowledge regarding the etiology and pathophysiology of disease, logic, personal experience, the opinions of colleagues or experts, textbooks, articles published in journals, and systematic reviews. An important principle of EBM is that the quality (strength) of evidence is based on a hierarchy. The precise hierarchy of evidence depends on the type of question being asked (Table 2-1).[11] This hierarchy consists of results of well-designed studies (especially if the studies have findings of similar magnitude and direction, and if there is statistical homogeneity among studies), results of case series, expert opinion, and personal experience, in descending order.[9,10] The hierarchy was created to encourage the use of the evidence that is most likely to be accurate and useful in clinical decision making. The ordering in this hierarchy has been widely discussed, actively debated, and sometimes hotly contested.[12]

A systematic review is an overview that answers a specific clinical question; contains a thorough, unbiased search of the relevant literature; uses explicit criteria for assessing studies; and provides a structured presentation of the results. A systematic review that uses quantitative methods to summarize results is a meta-analysis.[13],[14] A meta-analysis provides an objective and quantitative summary of evidence that is amenable to statistical analysis.[13] Meta-analysis is credited with allowing the recognition of important treatment effects by combining the results of small trials that individually lacked the power to demonstrate differences among treatments. For example, the benefits of intravenous streptokinase in treating acute myocardial infarction were recognized by means of a cumulative meta-analysis of smaller trials at least a decade before this treatment was recommended by experts and before it was demonstrated to be efficacious in large clinical trials.[15,16] Meta-analysis has been criticized because of the discrepancies between the results of meta-analysis and those of large clinical trials.[16-19] For example, results of a meta-analysis of 14 small studies of the use of calcium to treat preeclampsia showed a benefit to treatment,

whereas a large trial failed to show a treatment effect.[16] The frequency of such discrepancies ranges from 10 percent to 23 percent.[16] Discrepancies can often be explained by differences in treatment protocols, heterogeneity of study populations, or changes that occur over time.[16]

Publication bias is an important concern regarding systematic reviews. It results when factors other than the quality of the study are allowed to influence its acceptability for publication. Several studies have shown that factors such as sample size, direction and statistical significance of findings, and investigators' perceptions of whether the findings are “interesting” are related to the likelihood of publication.[20,21]

For example, in a study by Dickersin et al., the reasons given by investigators that results of completed studies were not published included “negative results” (28 percent), “lack of interest” (12 percent), and “sample size problems” (11 percent).[20] Results of studies with small samples are less likely to be published, especially if they have negative results.[20,21] This type of publication bias jeopardizes one of the main goals of meta-analysis (i.e., an increase in power through pooling of the results of small studies). Creation of study registers and advance publication of research designs have been proposed as ways to prevent publication bias.[22,23] Publication bias can be detected by using a simple

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graphic test (funnel plot) or by several other statistical methods.”[24,25] In addition, for many diseases, the studies published are dominated by drug company-sponsored trials of new, expensive treatments. The need for studies to answer the clinical questions of most concern to practitioners is not addressed because sources of funding are inadequate.

TABLE 2-1 Grades of Evidence[a],[b]

GRADE	LEVEL OF EVIDENCE	THERAPY/HARM	DIAGNOSIS
A	1a	Systematic review (with homogeneity[c]) of RCTs	Systematic review (with homogeneity) of level 1 (see column 2) diagnostic studies, or a CPG validated on a test set.
	1b	Individual RCT (with narrow confidence intervals)	Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have been evaluated by both the diagnostic test and the reference standard.
	1c	All or none[d]	Very high sensitivity or specificity
B	2a	Systematic review (with homogeneity) of cohort studies	Systematic review (with homogeneity) of level 2 or better (see column 2) diagnostic studies
	2b	Individual cohort study [including lowquality RCT (e.g., < 80% follow-up)]	Independent blind comparison but either in non-consecutive patients or confined to a narrow spectrum of study

			individuals (or both), all of whom have been evaluated by both the diagnostic test and the reference standard or a diagnostic CPG not validated in a test set
	2c	"Outcomes" research[e]	
	3a	Systematic review (with homogeneity) of case-control studies	Systemic review (with homogeneity) of 3b (see column 2) and better studies
	3b	Individual case-control study	Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients
C	4	Case series (and poor-quality cohort and case-control studies)	Reference standard was not applied independently or not applied blindly
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or logical	

deduction

CPG = clinical practice guideline, a systematically developed statement designed to help practitioners and patients make decisions about appropriate health care for specific clinical circumstances; RCT = randomized controlled trial.

[a]These levels were generated in a series of iterations among members of the NHS R&D Centre for Evidence-Based Medicine (Chris Ball, Dave Sackett, Bob Phillips, Brian Haynes, and Sharon Straus). For details see Levels of Evidence and Grades of Recommendation, http://www.cebm.net/levels_of_evidence.asp, May 2001.

[b]Recommendations based on this approach apply to “average” patients and may need to be modified in light of an individual patient's unique biology (e.g., risk, responsiveness) and preferences about the care he or she receives.

[c] *Homogeneity* means lacking variation in the direction and magnitude of results of individual studies.

[d] *All or none* means interventions that produced dramatic increases in survival or outcome, such as the use of streptomycin to treat tubercular meningitis.

[e] Outcomes research includes cost-benefit, cost-effectiveness, and cost-utility analysis.

Not all systematic reviews and meta-analyses are equal. A systematic review can be only as good as the clinical trials that it encompasses. The criteria for critically appraising systematic reviews and meta-analyses are shown in Table 2-2. Detailed explanations of each criterion are available.[13,26]

The type of clinical study that constitutes best evidence is determined by the category of question being asked. Questions about therapy and prevention are best

addressed by randomized controlled trials.[13],[26], [27], [28] Questions about diagnosis are best addressed by cohort studies.[13],[26],[29,30] Cohort studies, case-control studies, and post-marketing surveillance studies best address questions about harm.[13],[26],[31] Randomized controlled trials are a good source of evidence about the harmful effects of interventions for adverse events that occur frequently but not for rare adverse events. Case reports are often the first line of evidence regarding rare adverse events, and sometimes they are the only evidence. Methods for assessing the quality of each type of evidence are available.[13],[26]

With regard to questions about therapy and prevention, the randomized controlled clinical trial has become the gold standard for determining treatment efficacy. Thousands of randomized controlled trials have been conducted. Studies have demonstrated that failure to use randomization or to provide adequate concealment of allocation resulted in larger estimates of treatment effects, caused predominantly by a poorer prognosis in non-randomly selected control groups than in randomly selected control groups.[32] However, studies comparing randomized and nonrandomized clinical trials of the same interventions have reached disparate and controversial results.[32-34] Some found that observational studies reported stronger treatment effects than randomized controlled trials.[32] Others found that the results of well-designed observational studies (with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatment compared with randomized controlled trials on the same topic.[33,34] Examining the details of the controversy leads to the following limited conclusions. Trials using historical controls do yield larger estimates of treatment effects than do randomized controlled trials. Large, inclusive, fully blinded randomized controlled trials are likely to provide the best possible evidence about effectiveness.[12,35,36]

Although personal experience is an invaluable part of becoming a competent physician, the pitfalls of relying too heavily on personal experience have been widely documented.[7],[37],[38] Nisbett and Ross extensively reviewed people's ability to draw inferences from personal experience and describe several of these pitfalls.[39] These include the following:

- Overemphasis on vivid anecdotal occurrences and underemphasis on significant statistically strong evidence
- Bias in recognizing, remembering, and recalling evidence that supports pre-existing knowledge structures (e.g., ideas about disease etiology and pathogenesis) and parallel failure to recognize, remember, and recall evidence that is more valid

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TABLE 2-2 Critical Appraisal of a Systematic Review

- Are the results of this systematic review valid?
  - Did the review address a focused clinical question?[a]
  - Were the criteria used to select articles for inclusion appropriate?[a]
  - Is it unlikely that important relevant studies were missed?[b]
  - Was the validity of the included studies appraised?[b]
  - Were assessments of studies reproducible?[b]
  - Were the results similar from study to study?[b]
- Are the valid results of this systematic review important?
  - What are the overall results of the review?
  - How precise were the results?
- Can you apply this valid, important evidence in caring for your patient?
  - Can the results be applied to your patient's care?
  - Were all clinically important outcomes considered?
  - Are the benefits worth the harms and costs?

[a] Primary guides.

[b] Secondary guides.

From Sackett D et al: *Evidence-Based Medicine: How to Practice and Teach EBM*. Edinburgh, Churchill Livingstone, 1996.

- Failure to accurately characterize population data because of ignorance of statistical principles, including sample size, sample selection bias, and regression to the mean
- Inability to detect and distinguish statistical association and causality
- Persistence of beliefs in spite of overwhelming contrary evidence

Nisbett and Ross provide examples from controlled clinical research. Simple clinical examples abound. Physicians may remember patients whose condition improved, often assume that patients who did not return for follow-up got better, and conveniently forget the patients whose condition did not improve. A patient treated with a given medication may develop a severe life-threatening reaction. On the basis of this single undesirable experience, the physician may avoid using that medication for many future patients, although on average it may be more efficacious and less toxic than the alternative treatments that the physician chooses. Few physicians keep adequate, easily retrievable records to codify results of treatments with a particular agent or treatments of a particular disease; and even fewer actually carry out analyses. Few physicians make provisions for tracking those patients who are lost to follow-up. Therefore, statements made about a physician's "clinical experience" may be biased. Finally, for many conditions, a single physician sees far too few patients with the given disorder to allow reasonably firm conclusions to be drawn about the response to treatments. For example, suppose that a physician has treated 20 patients with lichen planus using tretinoin and found that 12 (60 percent) had an excellent response. The confidence interval for this response rate (i.e., the true response rate for this treatment in the larger population from which this physician's sample was obtained) ranges from 36 percent to 81 percent. Thus the true response rate might well be substantially less (or more) than the physician concludes from personal experience.

Expert opinion can be valuable, particularly when the disorder is a rare condition in which the expert has the most experience or when other forms of evidence are not available. However, several studies have demonstrated that expert opinion often lags significantly behind conclusive evidence.[7] Experts suffer from relying on bench research, pathophysiology, and treatments based on logical deduction from pathophysiology as well as from the same pitfalls noted for reliance on personal experience. Experts should be aware of the quality of the evidence that exists.

It is widely believed that clinical decisions can be made on the basis of an understanding of the etiology and pathophysiology of disease and logic.[1,10] This paradigm is problematic because the accepted hypothesis regarding the etiology and pathogenesis of disease changes over time. Therefore, the logically deduced

treatments change over time. For example, in the last 20 years, hypotheses about the cause of psoriasis have shifted from a disorder of keratinocyte proliferation and homeostasis, to abnormal signaling of cyclic adenosine monophosphate, to aberrant arachidonic acid metabolism, to aberrant vitamin D metabolism, to the current favorite, T-cell-mediated autoimmune disease. Each of these hypotheses spawned logically deduced treatments. The efficacy of many of these treatments has been substantiated by rigorous controlled clinical trials, but others are used even in the absence of systematically collected observations. Therefore, we have many options for treating patients with severe psoriasis (e.g., ultraviolet B radiation, narrow-band ultraviolet B radiation, Goeckerman treatment, psoralen plus ultraviolet A radiation, methotrexate, cyclosporin, and the biologics) and mild to moderate psoriasis (e.g., anthralin, topical corticosteroids, calcipotriene, and tazarotene) (see Chap. 18). However, we lack a clear sense of which is best, in what order they should be used, and in what combinations.[10,40] Treatments based on logical deduction from pathophysiology may have unexpected consequences. For example, the observation that antiarrhythmic drugs could prevent abnormal ventricular depolarization after myocardial infarction logically led to their use to prevent sudden death after myocardial infarction. However, a randomized controlled clinical trial showed increased mortality among patients treated with antiarrhythmic drugs than among those given a placebo.[28,41,42]

Textbooks can be valuable sources of evidence, particularly for rare conditions and for conditions for which the evidence does not change rapidly over time. However, textbooks have several well-documented limitations. They tend to reflect the biases and shortcomings of the experts who write them. Because of the way they are written, produced, and distributed, most are approximately 2 years out of date at the time of publication. Most textbook chapters are narrative reviews that do not consider the quality of the evidence reported.[7,13]

▪ FINDING THE BEST EVIDENCE

The ability to find the best evidence to answer clinical questions is crucial for the practice of EBM. Finding evidence requires access to electronic search tools, searching skills, and availability of relevant data. Evidence about therapy is the easiest to find. The most useful sources for locating the best evidence about treatment include the following:

- The Cochrane Library
- The MEDLINE (Medical Literature Analysis and Retrieval System OnLine) and EMBASE (*Exerpta Medica Database*) databases

- Primary journals
- Secondary journals
- Evidence-based dermatology and EBM books
- The National Guideline Clearinghouse (http://www.guideline.gov/)

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- The National Institute for Health and Clinical Excellence (http://www.nice.org.uk)

The Cochrane Library contains the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, the Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database, among other databases (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). Volunteers write the systematic reviews in the Cochrane Library according to strict guidelines developed by the Cochrane Collaboration. Issue 1, 2007, of the Cochrane Library contained 4655 completed systematic reviews. The number of reviews of dermatologic topics is steadily increasing.
The Database of Abstracts of Reviews of Effectiveness contains abstracts of systematic reviews published in the medical literature. It provides abstracts and bibliographic details on 5931 published systematic reviews. The Database of Abstracts of Reviews of Effectiveness is the only database to contain abstracts of systematic reviews that have been assessed for quality. Each abstract includes a summary of the review together with a critical commentary about the overall quality. The Health Technology Assessment Database consists of completed and ongoing health technology assessments (studies of the medical, social, ethical, and economic implications of health care interventions) from around the world. The aim of the database is to improve the quality and cost effectiveness of health care.

The Cochrane Library is the best source for evidence about treatment. It can be easily searched using simple Boolean combinations of search terms as well as more sophisticated search strategies. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Central Register of Controlled Trials, and Health Technology Assessment Database can be searched simultaneously.

The Cochrane Library is available on CD-ROM by personal or institutional subscription and on the World Wide Web from Wiley InterScience

(http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). Subscribers to the Cochrane Library are provided with quarterly updates. The Cochrane Library is offered free of charge in many countries by national provision and by many medical schools in the United States. It should be available at your medical library.

The second best method for finding evidence about treatment and the most useful source for finding most other types of best evidence in dermatology is searching the MEDLINE database by computer.[44,45] MEDLINE is the National Library of Medicine's bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the pre-clinical sciences. The MEDLINE database contains bibliographic citations and author abstracts from approximately 5000 current biomedical journals published in the United States and 80 foreign countries. The database contains approximately 15 million records dating back to the mid-1950s.[46]

MEDLINE searches have inherent limitations that make their reliability less than ideal.[45] Specific search strategies, or filters, have been developed to aid in finding relevant references and excluding irrelevant references to locate the best evidence about diagnosis, therapy, prognosis, harm, and prevention.[48]

These filters have been incorporated into the PubMed Clinical Queries search engine of the National Library of Medicine and are available at http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml.[49]

The use of PubMed Clinical Queries (http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml) is the preferred method for searching the MEDLINE database to locate the best clinically relevant evidence. It can be used freely by anyone with Internet access.

More than 20 vendors provide MEDLINE systems on-line and on CD-ROM. Haynes et al.[50] compared several vendors of MEDLINE on-line and on CD-ROM to determine which system was best in terms of locating relevant articles and excluding irrelevant articles. As assessed from combined rankings for the highest number of relevant and the lowest number of irrelevant citations retrieved, SilverPlatter MEDLINE clinical journal subset on CD-ROM performed best for librarian searches, whereas the PaperChase on-line system worked best for clinician searches. When judged by cost per relevant citation, Dialog's Knowledge Index performed best for both librarian and clinician searches.[50]

EMBASE is *Excerpta Medica's* database covering pharmacology and biomedical specialties.[13] EMBASE has better coverage of European and non-English language sources and may be more up to date.[13] The overlap in journals covered by MEDLINE and EMBASE is approximately 34 percent (range, 10 percent to 75 percent depending on the subject).[51],[52]

EMBASE is available on-line through the major database vendors [e.g., Data-Star, Dialog, DIMDI (Deutschen Institut für Medizinische Dokumentation und Information), Ovid Online, and STN]. For more information, see http://www.elsevier.com/wps/find/bibliographicdatabasedescription.cws_home/523328/description#description. Personal and institutional subscriptions are available.

Structured abstracts of articles are published in secondary journals (e.g., the Evidence-Based Dermatology section of *Archives of Dermatology*). The articles are strictly selected on the basis of methodologic quality and are accompanied by commentary putting the information in clinical perspective. *Evidence-Based Dermatology* (Williams H et al., editors, Oxford, Blackwell Publishing Ltd., 2002) is a compendium of "mini" systematic reviews of the treatment of skin diseases. *Clinical Evidence* is a compendium of evidence on the effects of common clinical interventions that is updated every 6 months. It is available through the American College of Physicians and the British Medical Association.

Full-text versions of many primary journals are now available on the Internet. Available vendors include DataStar, Dialog, DIMDI, Ovid Online, and STN, among others. The National Guideline Clearinghouse maintains a database of guidelines for the treatment of disease written by panels of experts following strict criteria for evidence. The database is accessible through the Internet (http://www.guidelines.gov). Current coverage of dermatologic topics is limited.

The National Institute for Health and Clinical Excellence produces guidance on public health, health technologies, and clinical practice based on the best available evidence. It is accessible online at http://www.nice.org.uk.

▪ CRITICALLY APPRAISING THE EVIDENCE

After evidence is found, the next step in practicing EBM is critically appraising the quality of the evidence and determining the magnitude of effects and the precision of the evidence. The criteria for critically appraising papers about treatment, diagnostic tests, and harmful effects of exposures are shown in Tables 2-3, 2-4, and 2-5, respectively.[13],[26] Papers that meet

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these criteria are more likely to provide information that is accurate and useful in the care of patients.[13,26] A detailed explanation of each criterion[13,26] and an example involving a patient with a dermatologic complaint are available.[45]

TABLE 2-3 Critical Appraisal of a Paper About Therapy

Are the results of this single preventive or therapeutic trial valid?

Was the assignment of patients to treatments randomized and was the randomization list concealed?

Were all patients who entered the trial accounted for at its conclusion and were their data analyzed in the groups to which they were randomly assigned?

Were patients and clinicians kept blind as to which treatment was being received?

Aside from the experimental treatment, were the groups treated equally?

Were the groups similar at the start of the trial?

Are the valid results of this randomized trial important?

Calculations:

Intervention Response Rate (IRR)	Comparison (Intervention) Response Rate (CRR)	Difference in Response Rates (DRR) (IRR — CRR)	Number Needed to Treat (NNT) (1/DRR)

What is the 95% confidence interval of the difference in response rates (DRR)?[a]

What is the 95% confidence interval of the NNT?[b]

Can you apply this valid, important evidence in caring for your patient?

Do these results apply to your patient?

Is your patient so different from those in the trial that its results can't help you?

How great would the potential benefit of therapy actually be for your individual patient?

Do the regimen and its consequences satisfy your patient's values and preferences?

Do your patient and you have a clear assessment

of your values and preferences?

Are this regimen and its consequences consistent with them?

[a] The 95% confidence interval of the DRR is from DRR - 1.96 × SE to DRR + 1.96 × SE

$$\text{DRR} - 1.96 \times \text{SE to DRR} + 1.96 \times \text{SE}$$

$$\text{where SE (standard error)} = \sqrt{\frac{IRR\,(1 - \text{IRR})}{\text{No. intervention patients}} + \frac{CRR\,(1 - CRR)}{\text{No. comparison patients}}}$$

[b] The 95% confidence interval of the NNT = 1/limits on the confidence interval of its DRR. From Sackett D et al: *Evidence-Based Medicine: How to Practice and Teach EBM*. Edinburgh, Churchill Livingstone, 1996.

TABLE 2-4 Critical Appraisal of a Paper About a Diagnostic Test

Are the results of this diagnostic study valid?

- Was there an independent, blind comparison with a reference (gold) standard of diagnosis?
- Was the diagnostic test evaluated in an appropriate spectrum of patients (like those in whom it would be used in practice)?

- Was the reference standard applied regardless of the diagnostic test result?

Are the valid results of this diagnostic study important?

Calculations:

		Target Disorder	
		Present	Absent
Diagnostic Test Result	Positive	a	b
	Negative	c	d

- Sensitivity = a/(a + c)
- Specificity = d/(b + d)
- Likelihood ratio for a positive test result = [a/(a + c)]/[b/(b + d)] = sensitivity/(1 - specificity)
- Likelihood ratio for a negative test result = [c/(a + c)]/[d/(b + d)] = (1 - sensitivity)/specificity

Can you apply this valid, important evidence about a diagnostic test in

caring for your patient?

- Is the diagnostic test available, affordable, accurate, and precise in your setting?
- Can you generate a clinically sensible estimate of your patient's pre-test probability (from practice data, from personal experience, from the report itself, or from clinical speculation)?
- Will the resulting post-test probabilities affect your management and help your patient? (Could it move you across a test-treatment threshold? Would your patient be a willing partner in carrying out your recommendations?)
- Would the consequences of the test help your patient?

From Sackett D et al: *Evidence-Based Medicine: How to Practice and Teach EBM*. Edinburgh, Churchill Livingstone, 1996.

Critically appraising evidence consists of the three steps of determining whether the results have each of the following characteristics:

- Validity (i.e., they are as unbiased as possible)
- Clinical importance
- Applicability to the specific patient being seen

Determining the validity of evidence centers on ascertaining whether the evidence was produced in a manner most likely to eliminate and avoid bias. The critical questions to ask to determine the validity of papers about therapy, diagnostic tests, and harmful effects are shown at the tops of Tables 2-3, 2-4, and 2-5, respectively.

Evidence About Therapy and Prevention

Studies of therapy should randomly assign patients to treatment groups (using a table of random numbers or pseudo-random numbers generated by computer) and ensure concealed allocation (e.g., by using opaque envelopes so that the treating physician cannot guess to which treatment group the patient has been assigned). In addition, there should be nearly complete follow-up of all patients entered into the study; intentionto-treat analysis of results; masking of investigators, patients, and statisticians where possible; equal treatment of groups; and similarity between treatment groups with regard to the distributions of prognostic variables. These criteria represent only a small subset of the features of a well-designed and wellreported clinical trial.[37] A more complete set of criteria has been published, and adherence to these criteria is required by many of the leading medical journals.[53]

Important terms and concepts that must be understood to determine whether the results of a paper about therapy are clinically important include the following:

- The magnitude of the treatment effect
- The precision of this value
- The difference in response rates
- Its reciprocal, the number needed to treat (NNT)
- The confidence interval

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TABLE 2-5 Critical Appraisal of a Paper About Harm

Are the results of this harm study valid?

- Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?
- Were treatment exposures and clinical outcomes measured the same ways in both groups? [For instance, was the assessment of outcomes either objective (e.g., death) or blinded to exposure?]
- Was the follow-up of study patients complete and long enough?

Do the results satisfy some “diagnostic tests for causation”?

- Is it clear that the exposure preceded the onset of the outcome?
- Is there a dose-response gradient?
- Is there positive evidence from a “dechallenge-rechallenge” study?
- Is the association consistent from study to study?
- Does the association make biologic sense?

Are the valid results from this harm study important?

Calculations:

		Adverse Outcome	
		Present (Case)	Absent (Control)
Exposed to the Treatment	Yes (cohort)	a	b
	No (cohort)	c	d

- In a randomized trial or cohort study, relative risk = [a/(a + b)]/[c/(c + d)].
- In a case-control study, odds ratio (or relative odds) = ad/bc.

Should these valid, potentially important results of a critical appraisal about a harmful treatment change the treatment of your patient?

- Can the study results be extrapolated to your patient?
- What are your patient's risks of the adverse outcome?
- What are your patient's preferences, concerns, and

expectations from this treatment?

- What alternative treatments are available?

From Sackett D et al: *Evidence-Based Medicine: How to Practice and Teach EBM*. Edinburgh, Churchill Livingstone, 1996.

In evaluating a clinical trial, the physician should look for clinical outcome measures that are clear-cut and clinically meaningful to the physician and his or her patients.[37] For example, in a study of a systemic treatment for warts, complete disappearance of warts is a meaningful outcome, whereas a decrease in the volume of warts is not. Historically, two principal methods have been used to determine patient outcomes in dermatologic clinical trials. The first involves examining the patient before, during, and at the conclusion of treatment and reporting how the patient appears at the various time points. The second involves determining the degree of improvement during treatment.[54] A third method, determining the impact of therapy on the quality of the patient's life, is being increasingly used in dermatologic trials.[37]

An example of the first method is commonly encountered in therapeutic trials of psoriasis. A common practice is to assign numerical values to the amount of erythema, the amount of scaling, the degree of infiltration, and the body surface area involved, and to formulate an “index” by calculating a derivative of some product of these four numbers.[55,56] The overall condition of the patient can then be represented by this index. A common index is the psoriasis area and severity index, which ranges from 0 to 72.[55] The major problem with indices is that they confound area of involvement with severity of disease.[54] For instance, a patient with thick plaque-type psoriasis of the knees, elbows, and scalp may have the same index as a patient with diffuse but minimal psoriasis of the trunk and arms. Whereas the former condition is notoriously difficult to treat, the latter will generally respond rapidly and easily to many forms of therapy.[54] The second problem with indices is that they lend an air of precision to the analysis and presentation of data that is not warranted.[54] For instance, Tiling-Grosse and Rees demonstrated that physicians and medical students were poor at estimating the area of involvement of skin disease, and therefore some of the components that make up indices may be inaccurate.[57]

Finally, calculations of the means, differences in means, and percentages of change in indices in response to treatment often do not convey an accurate clinical picture of the changes that have occurred.[54]

The second method of assessment groups patients according to their degree of improvement. Treatments are then compared in terms of their ability to move patients into categories representing higher degrees of improvement. There are two major problems with this form of assessment. The first is that the categories of improvement are often not well defined. The second problem is that the categories are not additive.[54] That is, 60 percent to 80 percent improvement is often assumed to be twice as good as 20 percent to 40 percent improvement, but no such numerical relationship exists between these subjectively defined categories.

To be most useful, the outcome variables to be measured must be clearly defined, must be as objective as possible, and must have clinical and biologic significance.[37],[54] The best indices and scales are the ones that accurately reflect the state of the disease and the ones whose validity and reliability have been verified by previous work.[37],[54,58] The development of scales and indices for assessing cutaneous diseases and the testing of their validity, reproducibility, and responsiveness have been inadequate.[37],[54,59] Therefore, a lack of clearly defined and useful outcome variables remains a major problem in interpreting dermatologic clinical trials.

Until better scales are developed, trials with the simplest and most objective outcome variables are the best. They lead to the least amount of confusion and support the strongest conclusions. Thus, trials in which a comparison is made between death and survival, recurrence of disease and no recurrence, or cure and lack of cure are studies whose outcome variables are easily understood and verified. For trials in which the outcomes are less clear-cut and more subjective, a simple ordinal scale is probably the best choice.[54] The best ordinal scales involve a minimum of human judgment, have a precision that is much smaller than the differences being sought, and are sufficiently standardized so that they can be used by others and produce similar results.[38]

In addition to being clearly defined, outcome variables should have clinical and biologic significance.[27,28] For example, in a therapeutic trial of patients with severe acne, treatment was associated with a decrease in lesion count from a mean of 400 to a mean of 350.

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This numerical difference may be of statistical significance, but it does not convey the biologic significance of the change in lesion number.[54] This result may mean that some patients with severe acne experienced complete clearance, whereas in others the acne remained the same or got worse. It could also mean that in most patients the acne got slightly better. Furthermore, does an individual patient look better when the lesion number has been reduced from 400 to 350? Is there less scarring and fewer complications?

To strengthen clinical trials and help validate their conclusions, investigators should select only a few outcome variables and should choose them before initiation of the study. Measurement of many outcome variables increases the likelihood that spurious, chance differences will be detected. An ineffective treatment may be found efficacious when tested using poorly designed outcome assessment tools. Conversely, an effective therapy may be found ineffective when an insensitive scale is used.

Special precautions are recommended to recognize and remain skeptical of substitute or surrogate endpoints, especially when no differences are detected in clinically important outcomes.[28,60] Examples of such endpoints include CD4/CD8 ratios instead of survival rates in studies of treatments for acquired immunodeficiency syndrome, anti-nuclear antibody levels or sedimentation rates instead of clinical measures of disease activity in lupus erythematosus, and volume of warts instead of proportion of patients cleared of warts. The use of carefully chosen and validated surrogate endpoints often allows studies to provide answers to questions that would typically require much larger or longer trials if the targeted clinical endpoint were used. For example, a well-designed short clinical trial may be sufficient to demonstrate that a new drug effectively lowers serum cholesterol level or that a given drug is effective in controlling hypertension. In both cases, much longer and larger studies would be required to demonstrate that the cholesterol-lowering drug and the antihypertensive drug reduced morbidity and mortality from atherosclerotic and hypertensive cardiovascular diseases, respectively. Surrogate endpoints must correlate with clinical outcomes, however, and their validity must have been demonstrated in prior studies.

Once sound, clinically relevant outcome measures are chosen, the magnitude of the difference between the treatment groups in achieving these meaningful outcomes should be determined. The precision of the estimate of the differences among treatments should be assessed. Useful measures of the magnitude of the treatment effect are the difference in response rate and its reciprocal, the NNT.[13,26,45] The NNT

represents the number of patients one would need to treat to achieve one additional cure.

The confidence interval provides a useful measure of the precision of the treatment effect.[13],[26],[45,61,62] The calculation and interpretation of confidence intervals have been extensively described.[63] In simple terms, the reported result (known as the *point estimate*) provides the best estimate of the treatment effect. Values become less and less likely as they move away from the reported result within the confidence interval.[13],[26],[45] The confidence interval provides a range of values in which the "population" or true response to treatment is likely to lie.

Examples of the application of the concepts of NNT and confidence interval are given in a paper identified through a search of the Cochrane Library that reported the results of a randomized controlled trial comparing the use of a placebo, acyclovir, prednisone, and acyclovir plus prednisone in the treatment of herpes zoster.[64] At day 30 of the trial, 48 of 52 patents treated with acyclovir experienced total healing compared with 22 of 52 patients who received a placebo. The response rates for acyclovir and placebo were 0.92 and 0.42, respectively, and the difference in response rates was 0.5. The NNT was 2 (1/0.5). This result means that for every two patients treated with acyclovir instead of placebo, one additional patient would show total healing by day 30. The 95 percent confidence interval for the difference in response rates is 0.35 to 0.65, and the 95 percent confidence interval for the NNT is 2 to 3.

What does it actually mean that the confidence interval for the difference in response rates in the foregoing example is 0.35 to 0.65? If the investigators in this study had the opportunity to repeat the study many times using the same design and procedures, sampling variability would prevent obtaining the same results in each study. Repeated trials were simulated using resampling (resampling is a computer-intensive method that uses the reported results of a trial to simulate the results that would be obtained if the trial were repeated a number of times).[45,65] The results when the trial was repeated 10 and 1000 times are shown in Fig. 2-1A and B, respectively. A 95 percent confidence interval of 0.35 to 0.65 means that if the trial is repeated many times and a confidence interval is calculated for each trial, the true result or response to treatment will be included in 95 percent of the confidence intervals so produced. Alternatively, if the trial were repeated multiple times, the results would lie within that interval (0.35 to 0.65) 95 percent of the time.

The population or true response to treatment will most likely lie near the middle of the confidence interval and will rarely be found at or near the ends of the interval.

The population or true response to treatment has only a 1 in 20 chance of being outside of the 95 percent confidence interval. Unless a given patient is very different from the patients included in the study, his or her response will most likely lie near the middle of the confidence interval. If the 95 percent confidence interval of the difference in response rates excludes zero difference, one can reject the null hypothesis that the two treatments are the same.[26,45,61,62]

Misinterpreting trials that fail to show statistically significant differences among treatments is a common error in dermatologic clinical trials. It is important to remember that "not statistically significant" means that a difference has a reasonably high probability of having been due to chance; it does not mean that there is no difference or that treatment is necessarily ineffective.[37] Significant differences in treatment effects in comparison trials may be missed if the number of subjects tested is small. For example, in a 1978 survey of 71 published trials with negative results, Freiman et al. found that a 25 percent or 50 percent improvement in outcome might have been missed in 57 (80 percent) and 34 (48 percent) of the studies, respectively.[66] A follow-up study conducted by Moher, Dulberg, and Wells in 1994 indicated that a 25 percent or 50 percent improvement in outcome might have been missed in 84 percent and 64 percent, respectively, of 102 studies with negative results.[67] The sample sizes of many dermatologic trials are often inadequate to detect clinically important differences.

The acceptance of a significance level of .05 as the cutoff for rejecting the null hypothesis is a tradition based on quality control standards and is not an absolute truth. At times (e.g., when treatments have substantial side effects)

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more stringent standards are required, and paradoxically, results that do not meet the p = 0.05 standard sometimes may be clinically significant. For example, consider a hypothetical trial of a new chemotherapeutic agent involving 30 patients with metastatic melanoma randomly assigned to treatment groups that produced a 5-year survival rate of 7 of 15 among patients treated with the new agent and 3 of 15 among control patients treated with conventional surgery, chemotherapy, and radiation. Whereas the result does not achieve statistical significance when analyzed by chi square testing (Yates corrected chi square = 1.35; p = 0.25), the result is nonetheless potentially significant. If the therapy is beneficial and the estimated difference in response rates is the true difference in response rates, it may result in the saving of 2400 lives annually (based on 7200 deaths from melanoma annually and

the improvement in survival in this hypothetical example). Because of the biologic and clinical importance of the results suggested by the trial, the treatment should be investigated in a study that uses a larger patient group and has more power to detect a significant difference if one exists.[37]

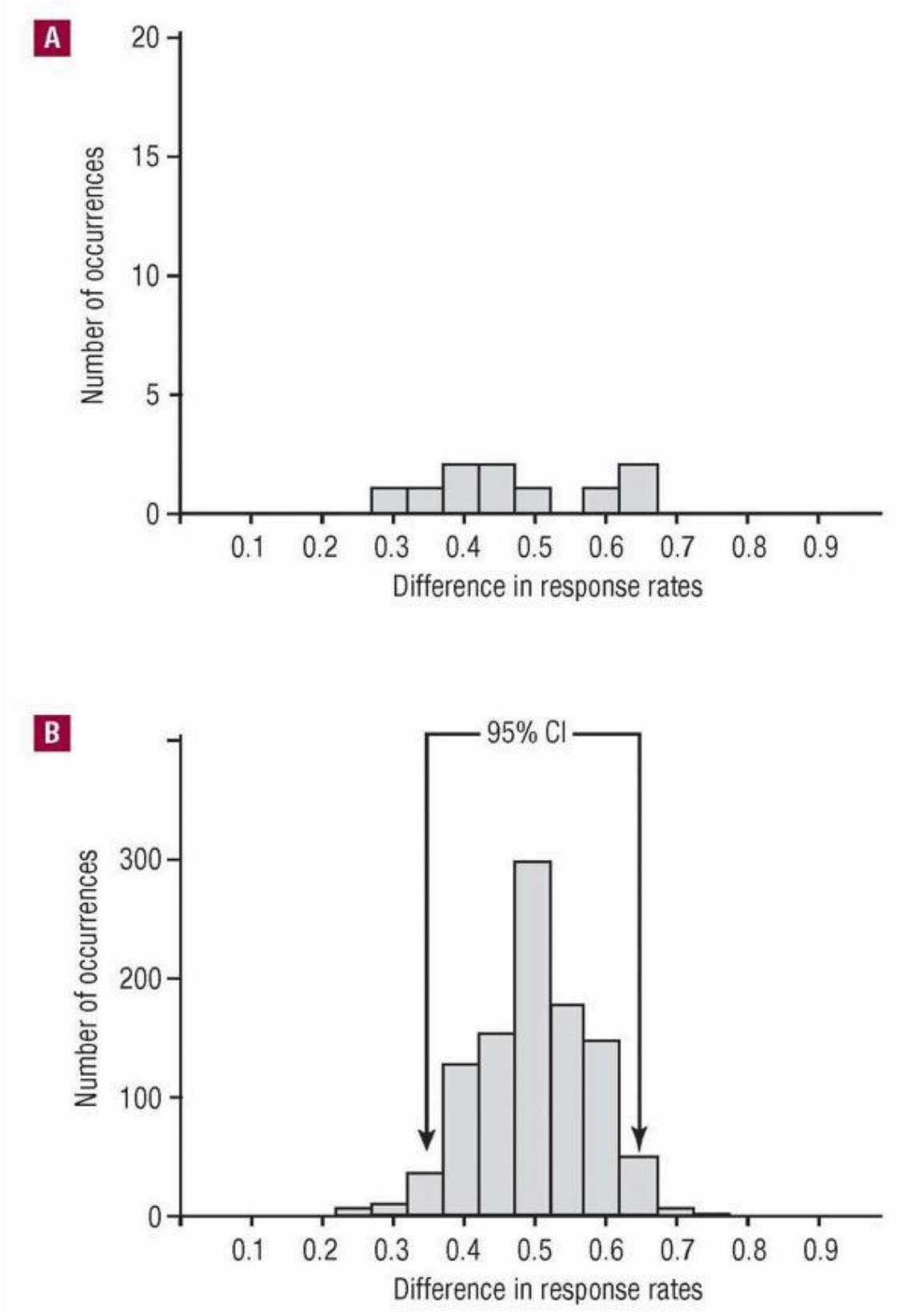


FIGURE 2-1 If the acyclovir trial were repeated 10 (**A**) or 1000 (**B**) times, the results

in **A** and **B,** respectively, might be obtained. Cl = confidence interval.

The potential benefit of the treatment may be further revealed by the use of confidence intervals. To determine whether a treatment effect may have been missed in a study reporting negative (not statistically significant) results, one should look at the upper boundary of the 95 percent confidence interval. If this value would be clinically important if it were the true response, then an important treatment effect may have been missed in the study. Consider our hypothetical new treatment for metastatic melanoma. The cure rates for the new treatment and the conventional treatment were 47 percent and 20 percent, respectively, and the difference between them was thus 27 percent. The 95 percent confidence interval for the difference in cure rates was -10 percent to 51 percent. The upper boundary of the difference in cure rates was 51 percent. This difference would clearly have a significant impact on the treatment of patients with metastatic melanoma (the NNT is 2!), and therefore a significant treatment advance may have been missed in this study. Also note that the 95 percent confidence interval of the difference in cure rates includes zero difference; therefore, we cannot conclude with a high degree of confidence that the response rates of the two treatments are different. However, when zero is included as one of the values in the confidence interval, the inference that the therapy is not efficacious fails to consider the fact that the best estimate of effect is the point estimate (e.g., the observed difference in cure rates of 27 percent in our hypothetical example).[68] In other words, the values contained in the confidence interval are not equally likely and become less and less likely as they move away from the point estimate. Thus, in the example, a difference of 25 percent (close to the observed 27 percent) is much more likely than a difference of -5 percent (far from the observed 27 percent).[37]

Evidence About Diagnostic Tests

To be valid, studies of diagnostic tests should include blind comparison with a criterion (gold) standard, evaluation in an appropriate spectrum of patients, and consistent application of the criterion standard. Few studies in dermatology meet these criteria.

Important terms and concepts that must be understood to determine whether the results of a paper examining a diagnostic test are clinically important include the following:

- Likelihood ratio

- Pre-test probability
- Post-test probability
- Threshold for action

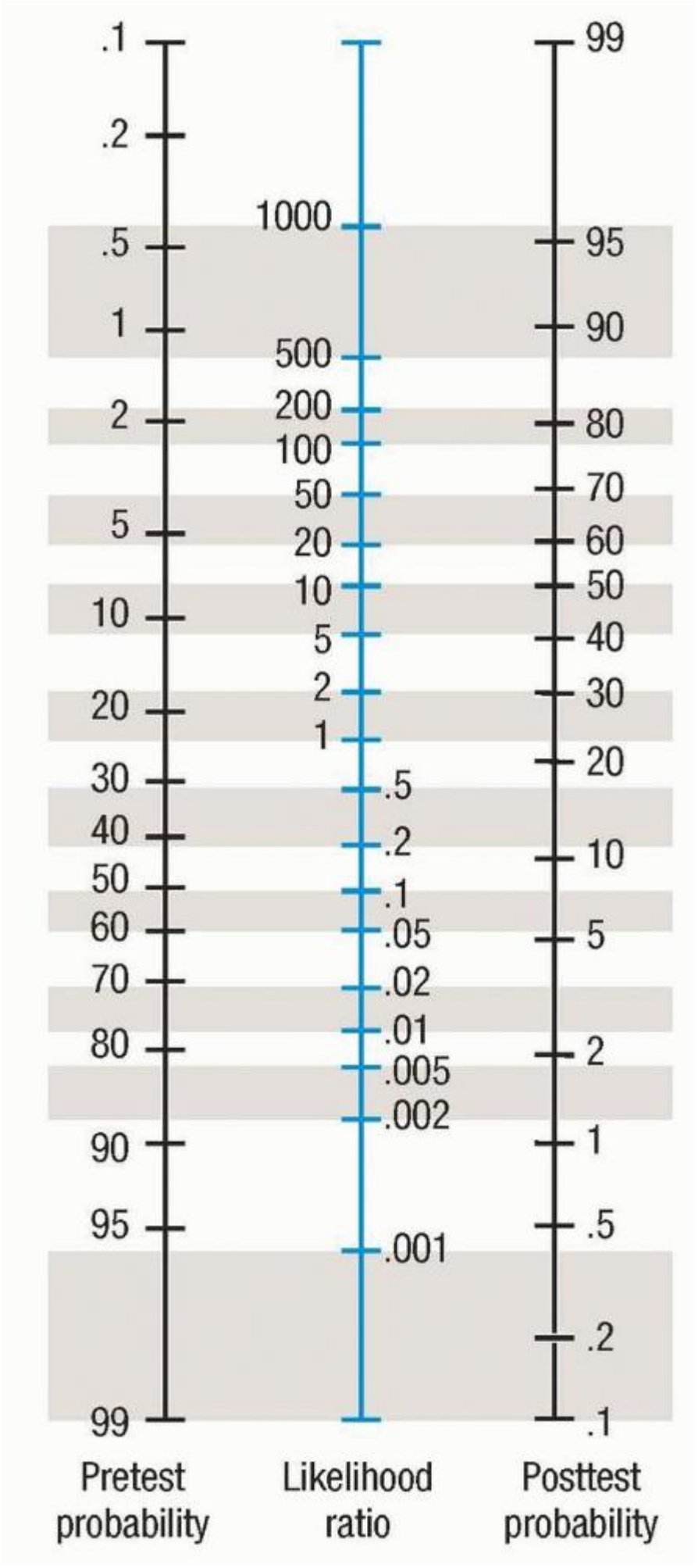
The likelihood ratio is the percentage of people with the given disease for whom the test result is positive divided
P.17

by the percentage of people who do not have the disease for whom the test result is positive.[45] The likelihood ratio is traditionally taught as the sensitivity divided by 1 minus the specificity [likelihood ratio = sensitivity/(1 - specificity)] and provides an estimation of how much higher the likelihood of the disease is, given a positive test result (post-test probability), compared with the probability before the test is done (pre-test probability).[13],[26] An ideal test is one that will almost always yield positive results when the disease is present and negative results when the disease is absent. Thus, it is one with a high sensitivity and specificity. Such a test will have a very high likelihood ratio.

For the likelihood ratio to be useful, one must have an idea of how likely it is that the disease is present before the test is done (i.e., the pre-test probability) and a sense of how certain one needs to be to conclude that the patient has the disease and to act on this information (i.e., the threshold for action).[45,69] The pre-test probability is determined from available published data or based on physician experience and judgment.[26],[45] Once the pre-test probability is known or estimated and the likelihood ratio is determined, a nomogram can be used to estimate the post-test probability (Fig. 2-2).[26]

If a nomogram is not available, the calculations can be done manually, but conversion of probabilities to odds is required. The odds of disease is defined as the probability of disease divided by 1 minus the probability [odds = probability/(1 - probability)]. For a defined group of individuals or patients, it can also be calculated as the ratio of the number of those with disease to those without disease. Thus, if the probability (proportion) of a disease is 0.20 (20 percent), the odds of that disease are 0.20/(1 - 0.20), or 0.20/0.80, or 1:4. This result means that for every person with the disease, there are four people without the disease. The post-test odds are equal to the pre-test odds times the likelihood ratio (post-test odds = pre-test odds × likelihood ratio).[26] The formula [probability = odds/(odds + 1)] is used to convert odds back to probability.

Whether formally or informally, physicians develop thresholds of certainty at or above which they are comfortable with establishing a diagnosis and acting on the diagnoses. Action may take the form of communicating the diagnosis or prognosis to the patient, prescribing treatment, or referring the patient. When historical and physical evidence leads a clinician to suspect a diagnosis but the degree of certainty does not exceed the threshold for establishing a diagnosis, a test is performed to raise the probability that the disease is present above the clinician's threshold for action.[69]


.1
.2
.5
1
2
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10
20
30
40
50
60
70
80
90
95
99
Pretest probability
1000
500
200
100
50
20
10
5
2
1
.5
.2
.1
.05
.02
.01
.005
.002
.001
Likelihood ratio
99
95
90
80
70
60
50
40
30
20
10
5
2
1
.5
.2
.1
Posttest probability

FIGURE 2-2 Nomogram for determining the post-test probability. To determine the post-test probability, draw a straight line through the pre-test probability and the likelihood ratio and read the post-test probability on the right.

Evidence About Harm

To be valid, studies about the harmful effects of exposures should include cohorts with comparable groups of exposed and unexposed individuals, or cases and controls; objective outcome measures; and adequate follow-up. In addition, the results should make clinical and biologic sense.[13],[26] Few dermatologic studies meet these criteria.

Important terms and concepts that must be understood to determine whether the results of a paper about harmful effects of exposures are clinically important include the following:

- Case-control and cohort studies
- Risk ratio
- Odds ratio

In a cohort study a group of individuals who are exposed to an agent is compared with an appropriately selected unexposed control group and both groups are followed until an event of interest occurs or for a pre-specified length of time. The association between exposure and the harmful outcome is expressed as the relative risk (see Table 2-5 for relative risk calculations). A relative risk of 1 implies no association. If the relative risk is greater than 1, then the result implies a positive association between exposure and the harmful outcome. If it is less than 1, then the implication is of an inverse association. However, to infer a causal association reflected by either an increase in risk (relative risk of more than 1) or a protective effect (relative risk less than 1), one must evaluate the validity and precision of the relative risk estimate. The precision can be readily assessed by means of the 95 percent confidence interval. A confidence interval that does not include 1.0 denotes a statistically significant association. Because the most likely result of a study is the point estimate (i.e., the reported result), the observed association (expressed by the point estimate) may be causal, even if the confidence interval includes 1.0 as a result of a small sample size.[13],[26]

Case-control studies are used when the bad outcome is recognized and the causative agent is not yet discovered. They are also used when there is a very long time lag between exposure and outcome or when the frequency of adverse events is very

small. In a case-control study, patients with a disease of interest are compared with appropriately selected controls. The odds of exposure to suspected etiologic agents are ascertained in cases and in controls (see Table 2-5). Recall that the odds of an event are calculated as the ratio of the number of events to the number of non-events.[70] Events are exposures to potentially harmful risk factors in case-control studies. The odds of exposure among cases are divided by the odds of exposure among controls to derive the odds ratio, which is a good estimate of the relative risk when the outcome (e.g., disease, death) is relatively rare (i.e., when it occurs in fewer than 5 percent of exposed subjects). The association between exposure

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and outcome is expressed as the odds ratio in case-control studies. An odds ratio of 1 implies no association. If the odds ratio is higher than 1, then the result implies a positive association between exposure and the harmful outcome. If the odds ratio is less than 1, then the result implies a protective effect of the exposure.[13],[26] As noted earlier, it is important to evaluate the validity and precision of the odds ratio estimate by examining the 95 percent confidence interval.

For example, suppose a case-control study was performed to study the relationship between limb deformity and exposure to thalidomide. The results of the study indicated that patients with limb deformities were more likely than controls to have been exposed to thalidomide in utero. The odds ratio for thalidomide exposure was 3.5 and the confidence interval was from 1.8 to 6.6. Thus the odds that patients with limb deformities were exposed to thalidomide in utero were 3.5 times the odds of thalidomide exposure in controls. Because the odds ratio is greater than 1 and its 95 percent confidence interval does not include 1, the result implies a positive association between thalidomide use and limb deformities not likely to have been due to random error. These results (an odds ratio of 3.5 and confidence interval of 1.8 to 6.6) were actually the findings of a study by Wolf et al., who studied the relationship between sunscreen use and melanoma in a case-control study in Austria.[71] Their results indicated that patients with melanoma were more likely than controls to have used sunscreen often. To infer causality it is important to assess whether the results could have occurred from bias and whether the results are biologically plausible.

To add confusion to an already difficult area, clinical researchers will often report results of meta-analyses, cohort studies, and randomized controlled trials using odds ratios. Odds ratios are used because they have stronger statistical properties than

other measures.[70] For example, odds ratios can take any value between 0 and infinity, are symmetric in a log scale, and can be used to make adjustments for confounding factors using multiple regression.[70] Unfortunately, they are the measure of association least intuitively understood. If a meta-analysis, controlled trial, or cohort study is reported using odds ratios, the relative risk, difference in response rates, or NNT can often be calculated if the primary data are provided. Alternatively, these more readily understandable measures can be derived if the number of subjects in each group, odds ratio, and overall event rate are provided.

▪ APPLYING EVIDENCE TO SPECIFIC PATIENTS

Applying the evidence to treatment of specific patients involves determining whether the evidence from studies is applicable to a given patient. This decision is based on the patient's condition and values. It involves asking a series of questions that are specific to the type of evidence being considered (see Tables 2-3, 2-4, and 2-5). When faced with the task of determining whether the results of a particular study are applicable to specific patients, physicians should determine whether there are any compelling reasons that the result should not be applied.[37] Applying evidence to specific patients always involves physician judgment.

▪ SAVING THE CRITICAL APPRAISAL OF THE EVIDENCE

Once the physician has made the effort to ask a clinical question, find the best evidence, and critically appraise it, the physician should save the analysis in a place and format that allows it to be easily retrievable for future use. Worksheets for recording evidence from papers dealing with diagnosis, therapy and prevention, prognosis, and harm are available (http://www.cebm.utoronto.ca/teach/materials/caworksheets.htm).[26] These worksheets can be saved electronically or filed physically.

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6.1.3 Chapter 3 - Public Health in Dermatology

Chapter 3

Public Health in Dermatology

Hywel C. Williams

Sinéad Langan

Carsten Flohr

▪ WHAT IS PUBLIC HEALTH MEDICINE ALL ABOUT?

Definition

The World Health Organization defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”[1] The key message of this definition is that health is a holistic measure that is influenced by socioeconomic factors and inequality. Public health is a discipline in which the level of focus is on the health of populations as opposed to that of individuals, as is the case in clinical medicine. A useful definition of public health is as follows:

Public health is the science and the art of preventing disease, prolonging life, and promoting physical health and mental health and efficiency through organized community efforts

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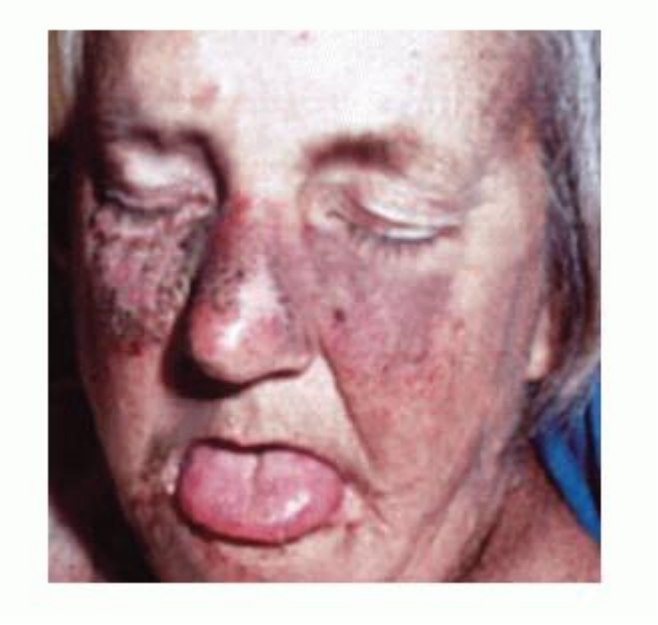
toward a sanitary environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and treatment of disease and the development of the social machinery to ensure to every individual in the community a standard of living adequate for the maintenance of health.[2]

PUBLIC HEALTH IN DERMATOLOGY AT A GLANCE



- Public health dermatology is about promoting skin health and not just treating skin disease.
- Despite strong historical origins, modern public health dermatology is still relatively underdeveloped.
- Doctors can do a lot to help individual patients but have little influence on the health of entire populations.
- Conversely, the impact of large population benefits are rarely appreciated by individuals.
- Prevention is often more logical than treating sick individuals who come for medical care.
- Sometimes a “low-risk” approach of reducing risk for diseases such as melanoma in the entire population can achieve more than a “high-risk” approach of targeting just those who have skin cancer or who are at high risk of developing skin cancer.
- When entire populations are considered, a little bit of harm affecting a lot of people can add up to more than a lot of harm affecting a few people in absolute terms.
- Modern public health dermatology has had some success in reduction of skin cancer incidence and control of infectious diseases.
- Sometimes, low-technology educational interventions directed at entire communities can result in more benefit than high-technology drugs targeted at a few ill individuals.

This definition articulates some of the roles of public health practitioners in relation to society and health. It also highlights the four key areas of public health action: (1) preventing disease and promoting health, (2) improving medical care, (3) promoting health-enhancing behavior, and (4) modifying the environment.[3]

Historical Perspectives

Public health has played a key role in the prevention and treatment of dermatologic diseases. One of the first historical examples is scurvy. In 1746, James Lind discovered through observation, analysis, and performance of a controlled trial that scurvy in sailors was a dietary disease that could be cured by administration of oranges and lemons[5] (see eFigs. 3-0.1 and 3-0.2 in on-line edition). Lind's treatise preceded the discovery of vitamin C by more than a century. In 1775, Percivall Pott was the first to describe an occupationally induced cancer by noting that the mortality from scrotal cancer was 200 times higher in chimney sweeps than in other workers.[6] He attributed the excess mortality to tar and soot exposure in combination with poor personal hygiene. The first carcinogenic polycyclic aromatic hydrocarbon was not discovered until 1933. In the early twentieth century, pellagra was a major public health problem (see eFig. 3-0.3 in on-line edition). There were 100,000 deaths from the disease in a 40-year period and over 3 million sufferers in the United States at that time. In 1914 Dr. Joseph Goldberger noticed that inmates at the Georgia State Sanatorium developed high rates of pellagra whereas the nurses and attendants did not, and concluded that the origin of pellagra was probably a disease caused by a dietary deficiency. He confirmed his hypothesis with controlled clinical trials.[7] The deficient dietary factor, niacin, was discovered in 1937.

Collectively these examples illustrate the importance of public health in the prevention of disease. These examples also highlight the fact that knowledge of disease pathophysiology (i.e., mechanisms) is not always a prerequisite to determining the cause or risk factors for a disease and the potential for effective public health interventions.

▪ HIGH-RISK AND LOW-RISK APPROACHES TO PUBLIC HEALTH

Traditionally, dermatology, like other branches of specialist medicine, has concentrated on the treatment of those who have fallen ill or those who believe they are ill or at high risk of developing disease. For instance, we prescribe topical corticosteroids for those with atopic dermatitis and we may give advice on sun protection to patients who previously had a malignant melanoma. We may see such melanoma patients on a regular basis in skin cancer follow-up clinics to monitor

treatment success and to be able to detect recurrences or new early second melanomas. Doctors and patients alike tend to be highly motivated when such an approach is used. The potential benefits seem obvious, and although there may be side effects associated with the prescribed treatment, such as skin thinning with prolonged use of topical corticosteroids, or a scar from excision of a melanoma, many patients will accept such risks, because appropriate treatment leads to a significant improvement of symptoms and improved quality of life or survival. Such an approach to tackling disease has often been referred to in the literature as the *high-risk* approach, because it focuses on the treatment and detection of those at high risk of developing disease and those who have already fallen ill.[8]

In contrast to the high-risk approach, the ultimate aim of public health medicine and public health dermatology is to prevent the development of disease in the first place whenever possible, not only by forestalling it in those identified as being at high risk (e.g., because of a strong family history), but by shifting the entire distribution of a certain exposure in a healthier direction for the whole population (population strategy). Such a low-risk approach can be implemented through large-scale public health education campaigns aimed at fundamentally changing the entire population's behavior and lifestyle. For example, based on the data of the Framingham study one can extrapolate that a reduction of everybody's blood pressure by 10 mm Hg would result in an overall reduction in mortality from heart disease of around 30 percent.[8] In dermatology, a good example of a such a population strategy is attempts to change the general population's sun exposure behavior to reduce exposure to ultraviolet light and ultimately skin cancer incidence and mortality through public health education campaigns that are national (e.g., Australia) or international (e.g., the World Health Organization's INTERSUN program, http://www.who.int/uv/intersunprogramme/en/) in scope (Fig. 3-1). This makes sense particularly in a country like Australia, because a strong association between ultraviolet

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radiation and melanocytic and non-melanocytic skin cancer is well established, and such risk is distributed widely through the predominantly fair-skinned population. Skin cancer is an important cause of death, and treatments for all forms of skin cancer pose an important burden on many countries' health care resources. Simple measures, such as avoiding sun exposure during peak hours of radiation and wearing suitable clothing, can provide adequate protection. The state of Victoria, Australia, has the most comprehensive population-based primary prevention campaign against

skin cancer in the world (SunSmart campaign, http://www.sunsmart.com.au/), and it has been reported that this program's public investment was worthwhile. Not only has it resulted in a significant reduction in skin cancer incidence and mortality, but the returns from savings on skin cancer treatments have also exceeded the overall costs of the SunSmart campaign.[9]

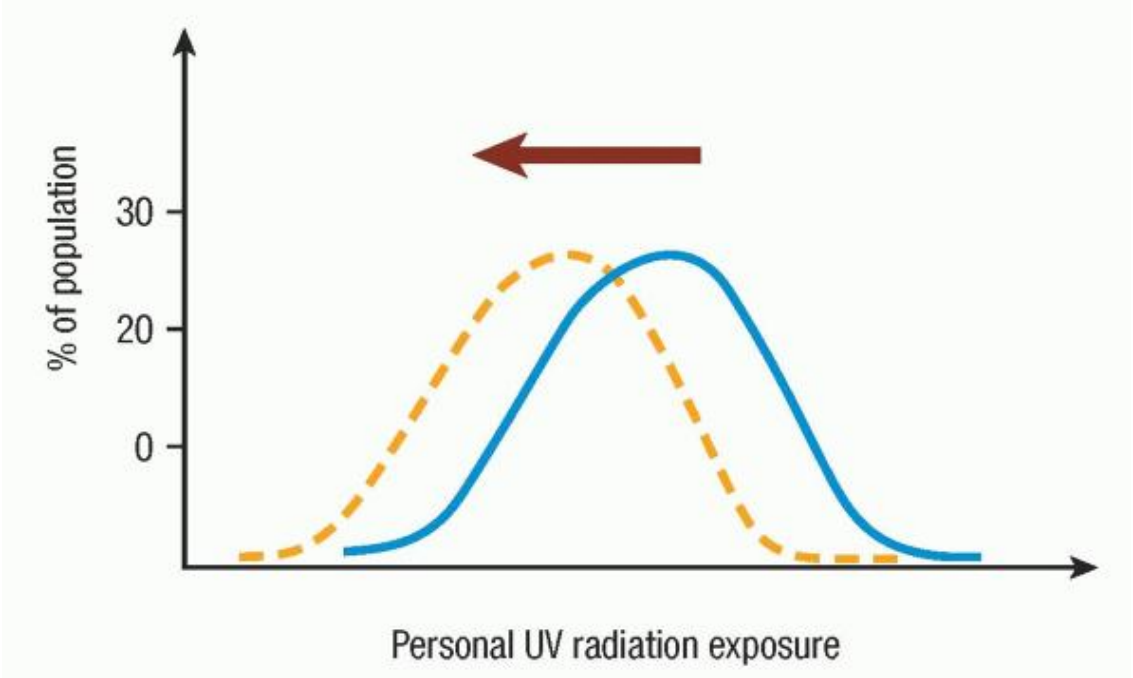

FIGURE 3-1 Distribution of ultraviolet (UV) radiation exposure before (*solid line*) and after (*dashed line*) implementation of a population strategy to reduce personal UV radiation exposure.

It may seem obvious that upstream prevention is more desirable than treating sick individuals who come for treatment downstream after a long chain of pathologic events, some of which may be irreversible. Funding population prevention strategies may be difficult, yet the whole population will potentially benefit, as long as such interventions are evidence based and sustainable. However, it is generally more difficult to persuade healthy individuals to protect themselves against prolonged sun exposure than to persuade those who have already had a malignant melanoma excised. It is also worth pointing out that although a public health intervention such as vaccination against measles has dramatically reduced the incidence of disease at a population level, it is impossible to say which individuals have been helped by such a population intervention—a phenomenon known as the *prevention paradox*.

A population strategy is not suitable for trying to control all skin diseases at present, because such a strategy depends on knowledge of modifiable risk factors. In the many cases for which exposures that predispose to a particular skin condition are unknown, prevention through avoidance is not possible, and the only option available is treatment of disease rather than primary disease prevention.

▪ A LOT OF HARM AFFECTING A FEW PEOPLE VERSUS A BIT OF HARM AFFECTING MANY

Making the conceptual jump from thinking about individual patients to thinking about entire populations can be challenging for practicing dermatologists, especially because such jumps can come up with some surprising results. For example, a dermatologist with an interest in contact dermatitis might see a case of severe hand dermatitis in a printer caused by allergic contact dermatitis from a chemical and then publicize such a case in a respected journal.[10] Another dermatologist reading such a case report might come to the conclusion that allergic contact dermatitis is an important cause of hand dermatitis in printers. Yet when this dermatologist visits the workplace to conduct a survey of all cases of hand eczema in printers, it becomes apparent that true allergic contact dermatitis is probably quite rare, and by far the most common cause of hand eczema is constant low-grade exposure to soap and water from repeated washing and friction from paper and dirt.[11] Thus, it is possible that a little bit of harm affecting a lot of individuals can add up to much more in absolute terms (the realm of the public health/occupational health physician) than a lot of harm affecting one or two workers (the realm of the dermatologist). Another well-known example of such a phenomenon is the effects of smoking on reduction in cardiovascular disease. Even though the association between tobacco smoking and lung cancer (relative risk of 14.0) is much stronger than that between smoking and cardiovascular disease (relative risk, 1.6), strategies for smoking cessation save around twice as many lives from cardiovascular disease than from lung cancer simply because heart disease is much more common than lung cancer.[12] From a public health perspective, therefore, the population-attributable risk (the proportion of the disease that may be attributable to a particular risk factor) is more important than other traditional measures of risk, such as the relative risk (whose magnitude may tell us something about the strength of a particular association). In a study of risk factors for psoriasis in Italy, Naldi et al. found that smoking accounted for up to 26 percent of all cases. In individuals with psoriasis who smoked who also had a family history of psoriasis, an increased body mass index might account for up to 48 percent of disease.[13] The fact that smoking

and obesity are modifiable risk factors suggests that psoriasis is preventable, at least to some degree, in this population.

▪ PUBLIC HEALTH APPROACH IN ACTION IN DERMATOLOGY

So far, we have illustrated the public health approach in dermatology using mainly historical examples. Yet although current dermatologic research is still relatively dominated by the pursuit of studies in which the unit of analysis is at a cellular or sub-cellular level, there are some good examples of public health dermatology in action.

One of the classic studies illustrating the public health approach in action for infectious skin disease was that conducted by Taplin and colleagues concerning scabies among Kuna Indians on the San Blas Archipelago.[14] These islands off the coast of Panama were plagued by very high rates of scabies in children in the 1980s, which led to misery and secondary bacterial infections. Despite the use of the best treatments available to combat the problem, the population burden of scabies remained largely unchanged. Only after the adoption of a public health approach in which everyone in defined areas was

treated did the prevalence of scabies fall dramatically from approximately 33 percent to approximately 1 percent. Similar dramatic decreases in scabies prevalence (from 25 percent to 1 percent) and in associated pyoderma and possibly post-streptococcal nephritis have been observed through the use of population-based treatment with ivermectin in the Solomon Islands.[15] Another example is the Global Alliance to Eliminate Lymphatic Filariasis (http://www.filariasis.org/), an alliance between the World Health Organization, ministries of health, and the private sector aimed at the worldwide eradication of this devastating disease. The Global Alliance to Eliminate Lymphatic Filariasis campaign is one of the most rapidly expanding public health programs in history and had regularly treated 25 million people in 12 countries by 2000 and 250 million in 39 countries by 2004. It is not restricted to mass treatment with antifilarial drugs but also includes public health education and advice on skin care of lymphedematous legs to prevent further morbidity.

Public health interventions are not restricted to administration of pharmaceutical drugs but can also include educational interventions such as the public education campaigns for reducing skin cancer through reduction in ultraviolet light exposure.

One such successful program has been the introduction of basic dermatologic care in Mali through the development of a training program for general health care workers on the management of common skin diseases.[16] The proportion of patients with skin disease with a clear diagnosis and appropriate diagnosis increased from 42 percent before the training to 81 percent after it. Although such dramatic effects might be overestimated in a simple before-andafter study, the effects were sustained for up to 18 months after training. Paradoxically, these improvements in care were associated with a 25 percent reduction in prescription costs, which suggests that inappropriate empirical prescribing was a source of unnecessary expenditure before the training. Other researchers have also documented how scarce family income can be wasted on inappropriate treatment for skin diseases such as pyoderma and scabies in Mexico.[17] Ryan has described the role of educational clinics in the prevention of skin cancers as well as the management of early lesions in the albino population of 170,000 in Tanzania.[18]

Although many public health interventions may not sound as “high tech” as drugs targeted at specific biologic receptors, they may be more effective and appropriate for sick populations. The concept that a little bit of harm affecting a lot of people can add up to more than a lot of harm affecting a few people was developed earlier, but a similar maxim also holds true: sometimes a low-technology beneficial intervention that can be applied to a large population can add up to far greater benefit in population terms than a high-technology solution that will benefit only a few.

▪ FUTURE OF PUBLIC HEALTH IN DERMATOLOGY

Some dermatologists have already conducted a population-based needs assessment for dermatologic care, followed by organization of the appropriate services at a population level, rather than just viewing the world of skin disease from within the narrow confines of a hospital-based practice. There are also increasing international collaborations to try to prevent and reduce the burden of skin diseases at a global level through health care planning and focused interventions. These are carried out through organizations such as the International Foundation for Dermatology (http://www.ifd.org/) in conjunction with the International League of Dermatological Societies (http://web.ilds.org/). The International League of Dermatological Societies is working to improve community dermatologic programs in developing countries, focusing on better diagnosis and clear evidence-based guidance for the management of common dermatoses. Training courses have been established, such as those at the Regional Dermatology Training Centre in Moshi, Tanzania (http://www.global-campus. org/rdtc) and short courses in Guerrero,

Mexico and Mali. One of the key aims of these programs is to educate at the primary care level with the idea that the trainees will then multiply such knowledge by training others in their own countries. As Weinstock points out in Chapter 1, the burden of skin diseases is high. Many skin diseases can already benefit from a public health approach. What is needed to redress the relative paucity of public health dermatology is to understand the concept that populations are as important as individuals and to build on the sort of collaboration championed by the International Foundation for Dermatology.

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6.2 Section 2 - Approach to Dermatologic Diagnosis

6.2.1 Chapter 4 - Structure of Skin Lesions and Fundamentals of Clinical Diagnosis

Chapter 4

Structure of Skin Lesions and Fundamentals of Clinical Diagnosis

Amit Garg

Nikki A. Levin

Jeffrey D. Bernhard

What is most difficult of all? It is what appears most simple: To see with your eyes what lies in front of your eyes.

—Goethe

▪ THE ART OF DIAGNOSIS

The diagnosis and treatment of diseases that affect the skin rest on the physician's ability to use the lexicon of dermatology, to recognize the basic and sequential lesions of the skin, and to recognize the various patterns in which they occur in a variety of diseases and syndromes. In this chapter, we discuss a fundamental approach to the patient presenting with a skin problem. We introduce the technical vocabulary of dermatologic description, the “dermatology lexicon”—a set of terms that denote types of skin lesions. It is important to know and use this standard terminology, as it is the first step in generating a differential diagnosis. Once a lesion has been described as a pearly, flesh-colored, telangiectatic, ulcerated nodule, the experienced physician puts basal cell carcinoma at the top of the differential diagnosis. It is also important to use standard dermatologic terminology for consistency in clinical documentation, in research, and in communication with other physicians.

The process of examining and describing skin lesions may be likened to that of viewing a painting. First, one stands back and takes in the whole “canvas,” analogous to viewing the patient from a few feet away at which distance an overall assessment of the patient's general and cutaneous health may be made. One may

note such findings as skin color and turgor, presence of pallor or jaundice, degree of sun damage, and the overall number and location of lesions. Next, one looks more closely at the “trees” or “mountains” that make up the landscape, analogous to describing and categorizing the specific lesions on the patient. Finally, one may closely examine the details of the canvas, taking in the texture and brushstrokes, analogous to using magnification to see the borders of a nevus or compressing a lesion to see if it blanches. Just as a knowledgeable viewer of art may recognize a work of Georges Seurat by its tiny, dot-like brush strokes, an experienced observer of the skin can recognize a melanoma by its asymmetry, irregular borders and multiple colors. This chapter aims to introduce the reader to the art and science of dermatologic diagnosis.

▪ APPROACH TO THE PATIENT

History

Dermatology is a visual specialty, and some skin lesions may be diagnosed at a glance. Nonetheless, the history is important and in complex cases, such as the patient with rash and fever or the patient with generalized pruritus, it may be crucial. Dermatologists vary in whether they prefer to take a history before, during, or after performing a physical examination. In practice, many perform a brief examination initially, obtain some history, then return to a more focused examination.

SKIN LESIONS AND DIAGNOSIS AT A GLANCE

- A patient and thorough approach to the evaluation decreases the risk of making an incorrect diagnosis or overlooking another diagnosis.
- Knowledge and appropriate use of dermatology terminology are fundamental.
- Recognition of disease patterns requires repeated patient encounters.
- The history is indispensable in elucidating complex diagnoses.
- The entire mucocutaneous surface, as well as the hair and nails, should be examined whenever reasonable.
- Morphologic characteristics derived from cell type in skin must be carefully scrutinized.
- Diseases have characteristic morphology and distribution.
- Common pitfalls in dermatologic diagnosis exist and can be avoided.

For the following reasons, it is often useful to at least briefly examine the patient before taking a lengthy history:

- Certain skin conditions, such as classic plaque-type psoriasis or molluscum contagiosum, for example, present with such distinctive morphologies

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that the diagnosis may be immediately obvious, rendering extensive history taking unnecessary.

TABLE 4-1 Approach to Dermatologic Diagnosis[a]

- Initial clinical impression: Does the patient appear ill?
- Physical examination: detailed examination of the skin, hair, nails, and mucous membranes
- Four cardinal features
  - Type of lesion: macule, papule, nodule, vesicle, etc. (see Table 4-2)
  - Shape of individual lesions: annular, iris, arciform, linear, round, oval, umbilicated, etc.
  - Arrangement of multiple lesions: isolated, scattered, grouped, linear, herpetiform, zosteriform, etc.
  - Distribution (be sure to examine scalp, mouth, palms, and soles)
    - Extent of involvement: circumscribed, regional, generalized, universal? What percentage of the body surface is involved?
    - Pattern: symmetry, exposed areas, sites of pressure, intertriginous areas?
- Characteristic locations: flexural, extensor, intertriginous, glabrous, palms and soles, dermatomal, trunk, lower extremities, exposed areas, etc.?
  - Three major characteristics
    - Color (see Table 4-3)

        - ~ If diffuse: red, brown, gray-blue, white, blue, orange-yellow, etc.; if circumscribed: red, violaceous, orange, yellow, lilac, livid, brown, black, blue, gray, white, etc.
        - ~ Does the color blanch with pressure (diascopy test)?
        - ~ Wood's lamp examination of pigmentary alterations: Is contrast enhanced?
      - Consistency and feel of lesion: soft, doughy, firm, hard, “infiltrated,” dry, moist, mobile, tender, warm?
      - Anatomic components of the skin primarily affected: Is the process epidermal, dermal, subcutaneous, appendageal, or a combination of these?
  - General physical examination as indicated by the clinical presentation and differential diagnosis, with particular attention to vital signs, lymphadenopathy, hepatomegaly, splenomegaly, joints, etc.
  - History of a rash. Key questions:
    - When did it start?
    - Does it itch, burn, or hurt?
    - Where on the body did it start?
    - How has it spread (pattern of spread)?
    - How have individual lesions changed (evolution)?
    - Provocative factors?
    - Previous treatments and response?
  - History of a growth. Key questions:
    - How long has the lesion been present?
    - Has it changed, grown, bled, itched, or failed to heal?
  - General history of present illness as indicated by clinical situation, with particular attention to constitutional and

prodromal symptoms
    - Acute illness syndrome (fever, sweats, chills, headache, nausea, vomiting, cough, runny nose, etc.)?
    - Chronic illness syndrome (fatigue, anorexia, weight loss, malaise)?
- Review of systems as indicated by clinical situation, with particular attention to symptoms indicating a possible connection between cutaneous signs and disease of other organ systems (e.g., rheumatic complaints: myalgias, arthralgias, Raynaud phenomenon, sicca symptoms)
- Review of systems for growths suspicious for, or associated with, malignancy: particular attention to symptoms of metastasis (weight loss, fevers, chills, night sweats, headache, swollen glands, abdominal pain, abnormal stooling, bone pain, etc.)
- Medication history: allergy; all prescription, nonprescription, and "complementary" medications, with particular attention to those that temporally correspond to the onset of the eruption
- Past medical history
    - Illnesses
    - Operations
    - Atopic history (asthma, hay fever, eczema)
    - Family medical history, particularly of skin disorders and of atopy
    - Family history of skin, or other, cancers
- Social history with particular reference to occupation, hobbies, sun exposure, pet exposure, tobacco smoking, alcohol consumption, recreational drugs, travel, sexual orientation and exposures
- Laboratory studies
    - Special procedures as determined by the individual clinical situation (see Chap. 5)
        - Dermatoscopy

        - Hand lens or 7 × loupe magnification for identifying specific features
        - Biopsy for histopathologic and other analyses (e.g., electron microscopy, immunofluorescence, special stains) if indicated
        - Tissue to be minced for bacterial and fungal cultures
        - Gram stains of crust, scale, or exudates
        - Potassium hydroxide preparation for yeast or fungi
        - Cytologic preparation (Tzanck smear) in vesicular and bullous eruptions
        - Swab for bacterial, viral, and fungal cultures
        - Wood's lamp examination of urine for porphyrins and of hair and skin for fluorescence or for changes in pigmentation
        - Oil mount preparation of scraping for scabies mite
        - Patch testing for allergic contact dermatitis
      - General: hematology, chemistry, urinalysis, serologic tests (e.g., syphilis, antinuclear antibody), imaging studies, and others as indicated by the presentation
    - Final diagnosis: re-examination over time and more than one biopsy may be required for definitive diagnosis

[a]This approach was developed by Thomas B. Fitzpatrick, Jeffrey D. Bernhard, and Harley A. Haynes. It has been modified by Amit Garg, Nikki Levin, and Jeffrey D. Bernhard.

- A patient's history may contain “red herrings,” which lead the physician away from, rather than toward, the correct diagnosis. Examination of the patient

before taking a history may yield a more complete and unbiased differential diagnosis.

- In certain situations, such as the evaluation of alopecia, initial examination of the patient to determine what type of hair loss is present allows the physician to pursue a line of questions pertinent to that type of alopecia.

In taking a history from a patient presenting with a new skin complaint, the physician's primary goal is to establish a diagnosis, with a secondary goal of evaluating the patient as a candidate for therapy. In patients whose diagnosis is already established, the physician's goals are to re-evaluate the original diagnosis, monitor disease progress and complications, and modify treatment accordingly. Table 4-1 is a guide useful in evaluating a patient with a rash or growth. The table is not an algorithmic

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method of arriving at a diagnosis. Rather, it is meant to provide the learner with a fundamental and general approach to diagnosing an unknown.

Examination of the Dermatologic Patient

SCOPE OF THE COMPLETE CUTANEOUS EXAMINATION

The complete cutaneous examination includes inspection of the entire skin surface, including often-overlooked areas such as the scalp, eyelids, ears, genitals, buttocks, perineal area, and interdigital spaces; the hair; the nails; and the mucus membranes of the mouth, eyes, anus, and genitals. In routine clinical practice, not all of these areas are examined unless there is a specific reason to do so, such as a history of melanoma or a particular localizing complaint.

ADVANTAGES TO PERFORMING A COMPLETE CUTANEOUS EXAMINATION

Although it is not always essential or practical to perform a complete skin examination, there are many advantages to doing so, especially for new patients and challenging cases:

- Identification of potentially harmful lesions (e.g., skin cancers) of which the patient is unaware; any patient with a history of skin cancer or a chief complaint of a “new growth” deserves a full skin examination.

- Identification of benign lesions (e.g., seborrheic keratoses, angiokeratomas) that the patient was concerned about but reluctant to mention, thereby enabling the physician to provide reassurance.
- Finding hidden clues to diagnosis (e.g., scabies lesions on the penis, psoriatic plaques on the buttocks, Wickham striae of lichen planus on the buccal mucosa, nail pitting in alopecia areata).
- Opportunity for patient education (e.g., lentigines are a sign of sun damage and suggest the need for improved sun protection).
- Opportunity to convey the physician's concern about the patient's skin health as a whole. Patients appreciate this and also regard the physician as thorough.

BARRIERS TO PERFORMING A COMPLETE SKIN EXAMINATION

Despite the advantages of performing a full cutaneous examination, numerous barriers exist that may prevent the dermatologist from performing such an evaluation for every patient. Understandably, patients may decline a full examination when their chief complaint is relatively minor or localized, such as a wart or acne. In other cases, patients may express resistance to disrobing for a full examination due to embarrassment, especially when the physician is of the opposite gender. Sometimes the physician is uncomfortable performing a complete skin examination with the concern that a patient may misinterpret the examination as improper. In many instances, time constraints and lack of personnel to serve as chaperones limit the ability to perform full skin examination.

IDEAL CONDITIONS FOR THE COMPLETE SKIN EXAMINATION

A complete skin examination is most effective when performed under ideal conditions. It is most important to have excellent lighting, preferably bright, even light that simulates the solar spectrum. Without good lighting, subtle but important details may be missed. The patient should be fully undressed, wearing only a gown that is easily moved aside, with a sheet over the legs, if desired. Underwear, socks, and shoes should be removed, as should any makeup or eyeglasses. The examining table should be at a comfortable height, with a head that reclines, an extendable footrest, and gynecologic stirrups. The examining room should be at a comfortable temperature for the lightly dressed patient. It should contain a sink for hand washing and disinfecting hand foam, as patients are reassured by seeing their physician wash hands before the examination. If the patient and physician are of opposite genders,

having a chaperone in the room can make the examination more comfortable for both.

RECOMMENDED TOOLS FOR THE COMPLETE SKIN EXAMINATION

Although the physician's eyes and hands are the only essential tools for examination of the skin, the following are often useful and highly recommended:

- A magnifying tool such as a loupe, magnifying glass, or dermatoscope.
- A bright focused light such as a flashlight or penlight to sidelight lesions.
- Glass slides or a hand magnifier for diascopy.
- Alcohol pads to remove scale or surface oil.
- Gauze pads or tissues with water for removing makeup.
- Gloves to be used for examination when scabies or another highly infectious condition (secondary syphilis) is suspected, when examining mucus membranes, vulvar and genital areas, and when performing any procedure.
- A ruler for measuring lesions.
- Number 15 and number 11 scalpel blades for scraping or incising lesions, respectively.
- A camera for photographic documentation.
- A Wood's lamp (365 nm) for highlighting subtle pigmentary changes.

TECHNIQUE OF THE DERMATOLOGIC PHYSICAL EXAMINATION

Just as there is no one correct way to perform a general physical examination, each physician approaches the complete skin examination with his or her own style. A common thread to effective styles of skin examination is consistency in the order of examining different body areas to ensure that no areas are overlooked. One approach to the complete skin examination is presented here. First, observe the patient at a distance for general impressions (e.g., asymmetry due to a stroke, obesity, pallor, fatigue, jaundice). Next, examine the patient in a systematic way, usually from head to toe, uncovering one area at a time to preserve patient modesty. Move the patient (e.g., from sitting to lying) and the illumination as needed for the best view of each body area. Palpate growths to determine whether they are soft, fleshy, firm, tender, or fluid-filled. Use of the hands to stretch the skin is especially useful in diagnosis of basal cell carcinoma, in which stretching skin reveals a “pearly” quality often not seen on routine inspection. A magnifier worn on the head leaves both hands free for palpation of lesions. Certain lesions, such as

porokeratosis, are best examined with side lighting that reveals depth and the details of borders. During the examination, patients often find it reassuring for the physician to name and demystify benign lesions as they are encountered.

Special examination techniques for hair disorders are discussed in Chap. 86, but include having the patient sit in a chair so that the entire scalp is easily examined, parting the patient's hair at the front and occiput and gently tugging on hairs to determine the fraction of loose (telogen) hairs. Examination of the nails is discussed in Chap. 87.

After completing the examination, it is important to document the skin findings, including the type of lesions and their locations, either descriptively or on a body map. Careful documentation is

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particularly important for suspicious lesions that are to be biopsied, so that the exact location may be found and definitively treated at a later date. Instant or digital photography is a useful adjunct for documentation.

▪ INTRODUCTION TO MORPHOLOGY

Siemens (1891-1969) wrote, “he who studies skin diseases and fails to study the lesion first will never learn dermatology.” His statement reinforces the notion that the primary skin lesion, or the evolution thereof, is the essential element on which clinical diagnosis rests. Joseph Jakob Edler von Plenck's (1738-1807) and Robert Willan's (1757-1812) work in defining basic morphologic terminology further permitted description and comparison of fundamental lesions, thereby facilitating characterization and recognition of skin disease. To read words, one must recognize letters; to read the skin, one must recognize the basic lesions. To understand a paragraph, one must know how words are put together; to arrive at a differential diagnosis, one must know what the basic lesions represent, how they evolve, and how they are arranged and distributed.

Variation and ambiguity in the morphologic terms generally accepted by the international dermatology community have engendered barriers to communication among physicians of all disciplines, including dermatologists. In dermatologic textbooks, the papule, for example, has been described as no greater than 1 cm in size, less than 0.5 cm, or ranging from the size of a pinhead to that of a split pea. Thus, in forming a mental image of a lesion or eruption after hearing its morphologic

description, physicians sometimes remain irresolute. The mission of the Dermatology Lexicon Project is to create a universally accepted and comprehensive glossary of morphologic descriptive terms to support research, medical informatics, and patient care (http://www.DermatologyLexicon.org). Morphologic definitions in this chapter parallel and amplify those of the Dermatology Lexicon Project. In describing morphologic terms, our intent is simple: to provide the reader with a pure appreciation of the "letters that make up the alphabet" rather than detailing a "field guide" for diagnoses, which are covered in depth throughout the textbook. Table 4-2 is a summary of the lesions discussed.

TABLE 4-2 Morphologic Lesions

RAISED	DEPRESSED	FLAT	SURFACE CHANGE	FLUID FILLED	VASCULAR
Papule	Erosion	Macule	Scale	Vesicle	Purpura
Plaque	Ulcer	Patch	Crust	Bulla	Telangiectasia
Nodule	Atrophy	Erythema	Excoriation	Pustule	Infarct
Cyst	Poikiloderma	Erythroderma	Fissure	Furuncle	
Wheal	Sinus		Lichenification	Abscess	

Scar	Striae	Keratoderma
Comedo	Burrow	Eschar
Horn	Sclerosis	
Calcinosis		

Raised Lesions

PAPULE

A papule is a solid, elevated lesion less than 0.5 cm in size in which a significant portion projects above the plane of the surrounding skin. Oblique lighting with a flashlight in a darkened room is sometimes necessary to detect the slight elevation of embedded papules. Papules surmounted with scale are referred to as papulosquamous lesions. Sessile, pedunculated, dome-shaped, flat-topped, rough, smooth, filiform, mammillated, acuminate, and umbilicated constitute some common shapes and surfaces of papules. A clinical example is lichen planus (Fig. 4-1; see Chap. 26).

PLAQUE

A plaque is a solid plateau-like elevation that occupies a relatively large surface area in comparison with its height above the normal skin level and has a diameter larger than 0.5 cm. The elevation need not be significant. Plaques, which may form by extension or confluence of papules, are further characterized by their size, shape, color, and surface change. A clinical example is psoriasis (Fig. 4-2; see Chap. 18).

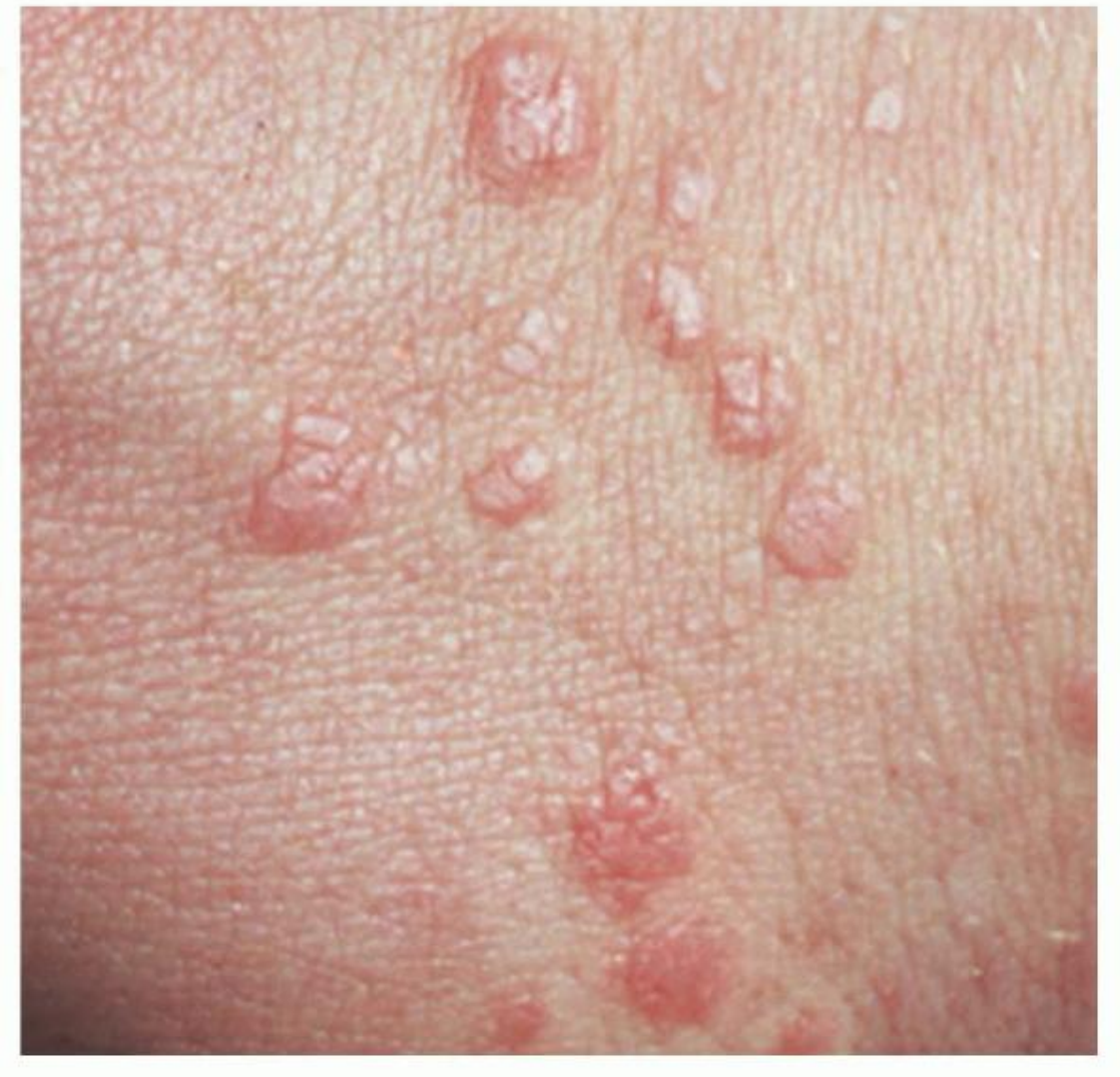

FIGURE 4-1 Papule. Multiple, well-defined papules of varying sizes are seen. Flat tops and glistening surface are characteristic of lichen planus.

NODULE

Depending on the anatomic component(s) primarily involved, nodules are of five main types: (1) epidermal, (2) epidermal-dermal, (3) dermal, (4) dermal-subdermal, and (5) subcutaneous. On the skin, a nodule is a solid, round or ellipsoidal, palpable lesion that has a diameter larger than 0.5 cm. Size, however, is not the major consideration in the definition of nodule. Depth of involvement and/or substantive palpability, rather than diameter, differentiates a nodule from a large papule or plaque. *Tumor,* also sometimes included under the heading of nodule, is a general term for any mass, benign or malignant. A *gumma* is, specifically, the granulomatous

nodular lesion of tertiary syphilis. For cases in which more than one term may be applicable, it is simply best to include measurements and descriptive terms that convey the important features of the lesion in question. Some additional features of a nodule that may help reveal a diagnosis include whether it is warm, hard, soft, fluctuant, movable, fixed, or painful. Similarly, different surfaces of nodules, such as smooth, keratotic, ulcerated, or fungating, also help direct diagnostic considerations. A clinical example is nodular basal cell carcinoma (Fig. 4-3; see Chap. 115).

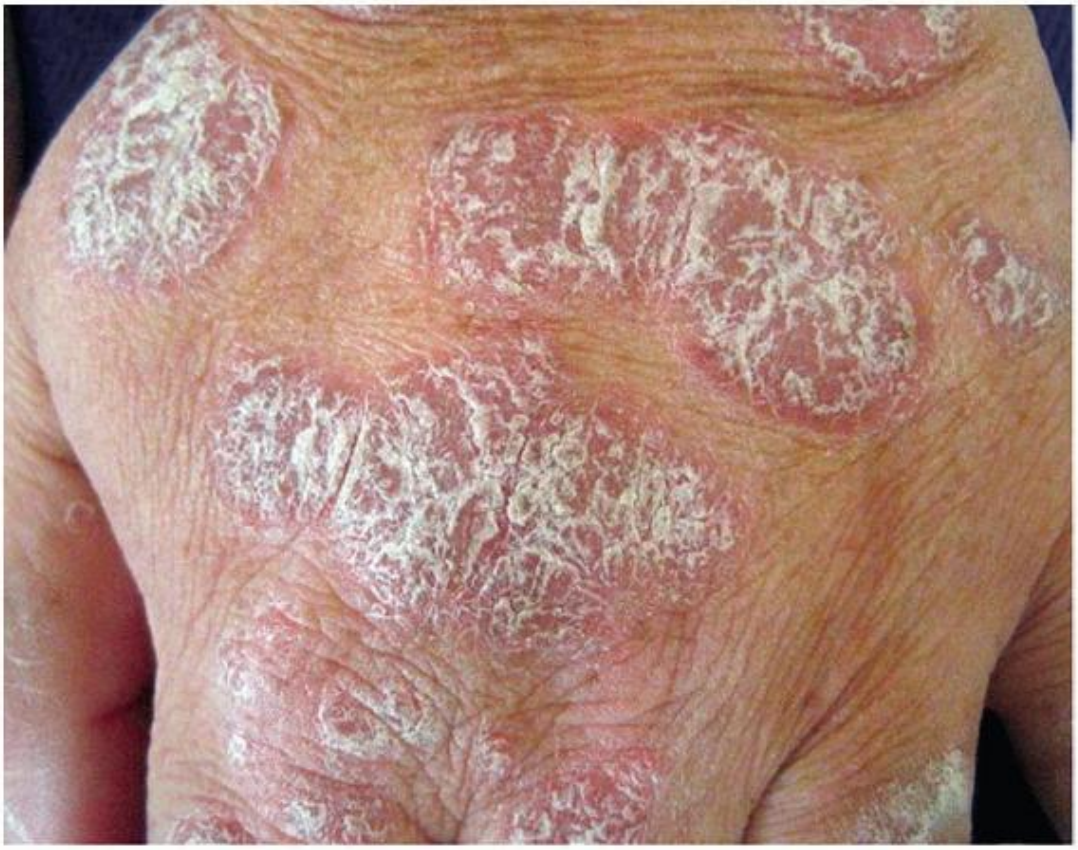

FIGURE 4-2 Plaque. Well-demarcated pink plaques with a silvery scale representing psoriasis vulgaris.

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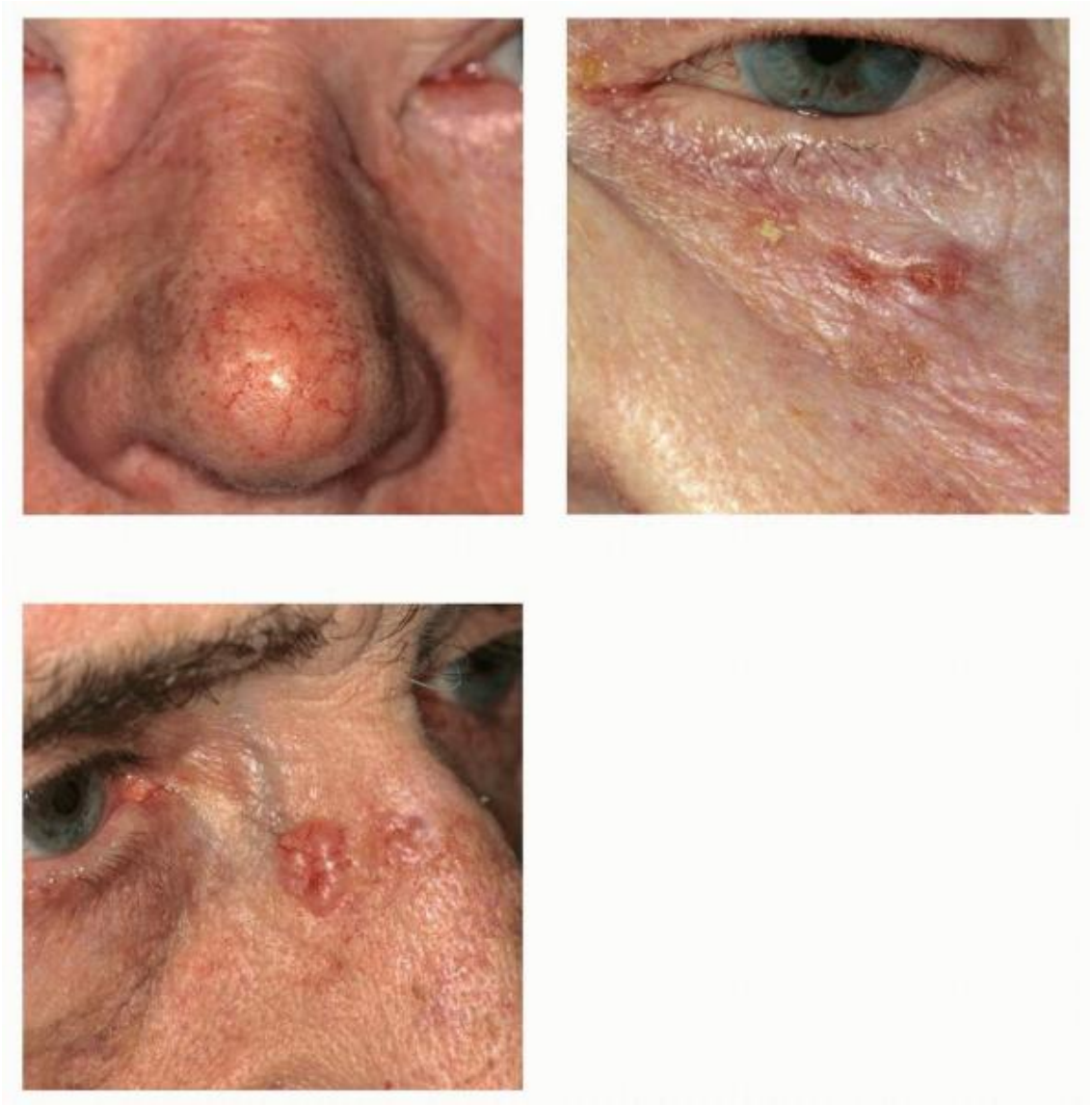

FIGURE 4-3 Nodule. A nodular basal cell carcinoma with well-defined, firm nodule with a smooth and glistening surface through which telangiectasia can be seen.

CYST

A cyst is an encapsulated cavity or sac lined with a true epithelium that contains fluid or semisolid material (cells and cell products such as keratin). Its spherical or oval shape results from the tendency of the contents to spread equally in all directions. If the overlying skin is stretched enough by the cyst, follicular openings may be prominent. Sometimes, the cavity is so superficial that it gives the appearance of a vesicle that lacks encapsulation. A nodule or papule may be suspected of being a cyst if, on palpation, it is resilient; the eyeball, for example,