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Volume One

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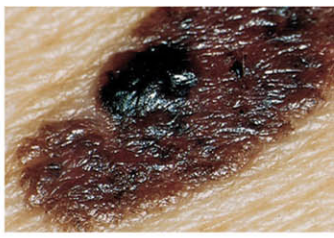

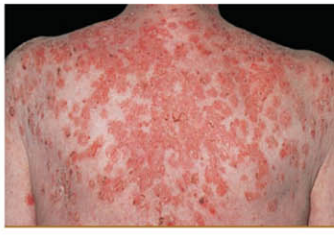

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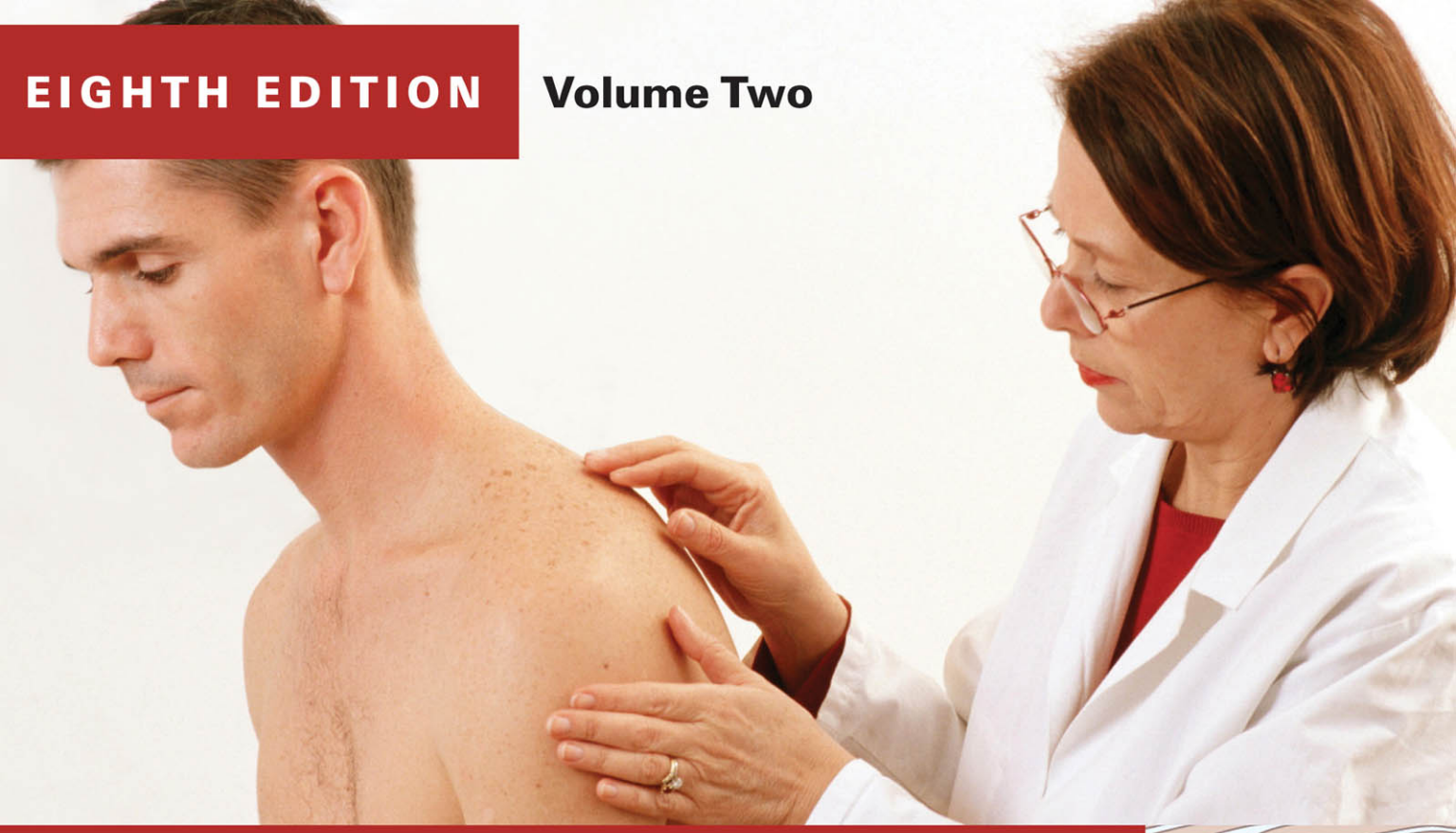

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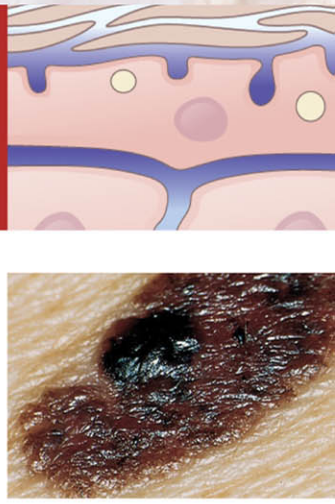

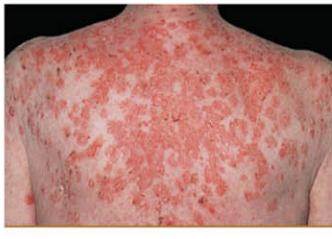

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Fitzpatrick's Dermatology in General Medicine

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Fitzpatrick's Dermatology in General Medicine

Eighth Edition

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PREFACE

New knowledge drives medical progress and improves patient care. The rapid growth of this knowledge in skin diseases and skin biology makes publication of the eighth edition of *Fitzpatrick's Dermatology in General Medicine* (DIGM) particularly timely. Forty years ago, the first edition of "*Fitz*" was a critical textbook devoted to providing a comprehensive knowledge of dermatology. The relevance of dermatology to general medicine and the basic science foundations of the specialty were defining elements of the new text. This edition, more than ever, reinforces those earlier goals and is designed to be easily accessible to those interested in the clinical and basic science of dermatology. This reference text also highlights the relevance of dermatology to general internal medicine and other disciplines of medicine and surgery. It is written for experienced clinicians and skin biologists worldwide as well as for those in training.

The online edition adds further textual and illustrative detail to almost all chapters and provides extensive and robust literature citations, many with online links, which are especially useful for those who seek an in-depth understanding of a particular topic. The accompanying CD-ROM contains the figures from the print edition in an easily downloaded format for slide production.

Because of the explosion of new knowledge relevant to dermatology and cutaneous biology, chapters have been extensively revised and new chapters have been added on global dermatologic health, ethnic, and racial considerations for normal and diseased skin, and stem cell science. Medical and surgical therapeutics sections have been greatly expanded to reflect the increased importance of procedural dermatology.

Twenty percent of the chapters have new authorship, drawing from expertise around the world. These authors provide new perspectives and guarantee that the content of the book remains fresh and vital.

Schematic diagrams of clinical and basic science mechanisms and clinical care algorithms have been revised to allow rapid intuitive guidance while retaining accuracy and critical detail. This edition is enhanced with additional clinical figures and new tables that permit a "quick look" at key points in each chapter. Finally, the Parts of the book are designated with different colors, thus allowing the reader to easily find sections of interest.

Validated, well-synthesized, and critically interpreted information is essential to improve the care of patients, to prevent skin disease, and to advance cutaneous biology. The current editors of DIGM have striven to fulfill these goals of the original text.

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ACKNOWLEDGMENTS

We thank and salute the nearly 500 authors who contributed to the creation of this new and vibrant eighth edition of *Fitzpatrick's Dermatology in General Medicine* (DIGM). The eighth edition of this classic text reflects the amazing growth in new knowledge in basic and clinical sciences related to the skin and to its relationship with other organ systems. The authors have worked assiduously to integrate this new information within the context of established knowledge. The authors, all respected experts in their disciplines, wrote some of the most extensively referenced chapters available either in print or online. We are deeply grateful to them and their staff for their commitment to this text. Their expertise has created chapters that continue to define the comprehensiveness of this textbook.

We are deeply grateful to our families, who appreciated the importance and immensity of our task. They recognized and accepted that editing this textbook demanded many hours of time and evenings spent with a computer screen rather than with them. We thank them for their support during this all-consuming effort.

The editors were supported by talented and dedicated staff, Renate Kosma, Jacy Bernal, Jaime Zagami, Nilda Reyes, and Grace Camire, each of whom handled the correspondence with over 50 authors. The debt that we owe to these individuals cannot be calculated. Many readers of previous editions and dermatology residents from several training programs painstakingly reviewed and critiqued the seventh edition and provided extremely useful advice on improving the content and the presentation for this new edition.

The staff at McGraw-Hill Medical made this text their highest priority. They were led by our ever vigilant and talented editor, Anne M. Sydor, and our project manager for manuscript production and completion, Sarah M. Granlund; and a most professional production team led by Robert Pancotti and Sherri Souffrance in New York and by Sandhya Joshi in India.

A major hallmark and the fresh look for this eighth edition are the hundreds of new figures that required meticulous attention by authors and a creative design and art team at Dragonfly Media Group. For their talented and effective partnership we are forever grateful.

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PART 1 Introduction

General Considerations

Chapter 1 :: The Epidemiology and Burden of Skin Disease

:: Martin A. Weinstock & Mary-Margaret Chren

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.[1–3]

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, accessed Jul 7, 2010) and adopted by leading dermatology journals to improve assessment of their validity and their use in subsequent systematic reviews[5] (see Chapter 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 some 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 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 Section "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 Chapter 4). The Centers for Disease Control and Prevention has outlined this framework as a series of ten steps, which are described in more detail at http://www.cdc.gov.

1. *Preparation*. Before initiating fieldwork, background information on the disease must be gathered, and appropriate interinstitutional and interpersonal contacts should be made.
2. *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.
3. *Confirm the diagnosis*. Symptoms and signs of persons affected should be determined and laboratory findings confirmed, perhaps with the assistance of reference laboratories.
4. *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 are key to defining the scope of the outbreak.
5. *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.
6. *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.
7. *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.
8. *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.
9. *Implement control measures*. As soon as the causal chain of events is understood, prevention and control measures are initiated.
10. *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 Jul 7, 2010) 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 2006, there were 16,163 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 less than 2% of these deaths. The total number of skin disease deaths, of course, depends critically on the definition of skin disease, as noted in Section "Descriptions of Disease in Populations: Measures of Disease Burden."

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 US population standard, the result is 50% higher than when the 1940 US 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 are reported, the reader must be wary of different definitions that may be applied. In one analysis, a decline in years lost from melanoma was noted by one definition that was not observed with another.[13]

TABLE 1-1
Skin Disease Deaths, United States, 2006

Disease	Deaths (*n*)
Cancers	12,301
Melanoma	8,441
Genital	1,126
Lymphoma	91[a]
Other cancers	2,643[a] (primarily basal and squamous cell carcinoma)
Ulcers	1,496
Infections	1,793
Bullous disorders	269
Other causes	304
Total	16,163

[a]We estimate that approximately one-half of keratinocyte carcinoma deaths are misclassified squamous cell carcinomas arising from mucosal surfaces in the head and neck[16] and that cutaneous lymphoma deaths are underestimated by a factor of 2 (see text). [Adapted from http://wonder.cdc.gov/ (verified Apr 27, 2010).]

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 conventional estimates of deaths from cutaneous lymphoma miss about half of the actual deaths.[18]

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 underreporting 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 underreporting remains a potential concern with these data.[19,20] Special surveys have been conducted and administrative datasets analyzed to estimate incidence of other disorders, such as keratinocyte carcinomas, although a system of sentinel registries would improve nationwide assessment.[21,22] 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.[23,24] Specific contexts that permit more accurate incidence estimates include the workplace; for example, where occupational skin disease is a prevalent problem.[25]

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

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

	1940	1950	1960	1970	1980	1990	2000	2008
Acquired immunodeficiency syndrome	NA[a]	—	—	—	—	41,595	40,758	39,202
Anthrax	76	49	23	2	1	0	1	0
Congenital rubella	—	—	—	77	50	11	9	0
Congenital syphilis	—	—	—	—	—	3,865	529	227
Diphtheria	15,536	5,796	918	435	3	4	1	0
Gonorrhea	175,841	286,746	258,933	600,072	1,004,029	690,169	358,995	229,315
Hansen disease	0	44	54	129	223	198	91	72
Lyme disease	—	—	—	—	—	—	17,730	26,739
Measles	291,162	319,124	441,703	47,351	13,506	27,786	86	132
Plague	1	3	2	13	18	2	6	1
Rocky Mountain spotted fever	457	464	204	380	1,163	651	495	2,276
Syphilis (primary and secondary)	—	23,939	16,145	21,982	27,204	50,223	5,979	12,195
Toxic shock syndrome	—	—	—	—	—	322	135	66
Tuberculosis[b]	102,984[c]	121,742[c]	55,494	37,137	27,749	25,701	16,377	9,795
US population (millions)	132	151	179	203	227	249	281	304

[a]NA = data not available.
[b]Reporting criteria changed in 1975.
[c]Data include newly reported active and inactive cases.
Adapted from Weinstock MA, Boyle MM: Statistics of interest to the dermatologist. In: *The Year Book of Dermatology and Dermatologic Surgery, 2009*, edited by B Theirs, PG Lang. Philadelphia, Elsevier Mosby, 2009, p. 53-68.

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.

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.[26] Despite its limitations, this study was notable because the sample was representative of the general US 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 gender-specific prevalence are indicated in Table 1-3 and Fig. 1-1. A similar survey in the United Kingdom of over 2,000 Londoners in 1975 noted that almost one-quarter of adults had a skin condition serious enough to warrant medical care.[27] Other efforts have focused on obtaining prevalence estimates of specific conditions with special surveys.[28,29]

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.[30]

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 1,000 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, US Department of Health, Education, and Welfare, November 1978.

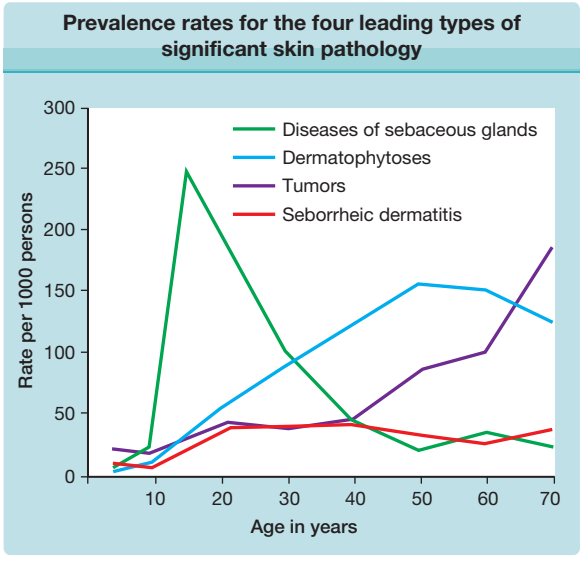

Figure 1-1 Prevalence rates for the four leading types of significant skin pathology among persons 1–74 years, by age, in the United States, 1971–1974.

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

OTHER MEASURES OF MORBIDITY: CONCEPTUAL ISSUES

The consequences of skin disease for a population (or the *burden of disease*) are complex; a practical conceptu-

TABLE 1-4
Visits to Non-Federal Office-Based Physicians in the United States, 2006[a]

	Type of Physician		
Diagnosis	Dermatologist[b]	Other	All Physicians
Acne vulgaris	2,217 (8.8%)	[b]	3,274 (0.4%)
Eczematous dermatitis	3,183 (12.6%)	5,377 (0.6%)	8,560 (1.0%)
Warts	1,041 (4.1%)	1,361 (0.2%)	2,401 (0.3%)
Skin cancer	2,672 (10.6%)	928 (0.1%)	3,599 (0.4%)
Psoriasis	692 (2.7%)	[b]	737 (0.1%)
Fungal infections	[b]	1,759 (0.2%)	2,002 (0.2%)
Hair disorders	741 (2.9%)	[b]	1,571 (0.2%)
Actinic keratosis	2,432 (9.6%)	[b]	2,717 (0.3%)
Benign neoplasm of the skin	1,293 (5.1%)	[b]	2,170 (0.2%)
All disorders	25,256 (100%)	876,698 (100%)	901,954 (100%)

[a]Estimates in thousands.
[b]Figure does not meet standard of precision.
Note: Percentage of total visits is in parentheses.
Adapted from Weinstock MA, Boyle MM: Statistics of interest to the dermatologist. In: *The Year Book of Dermatology and Dermatologic Surgery, 2009*, edited by B Theirs, PG Lang. Philadelphia, Elsevier Mosby, 2009, p. 53-68.

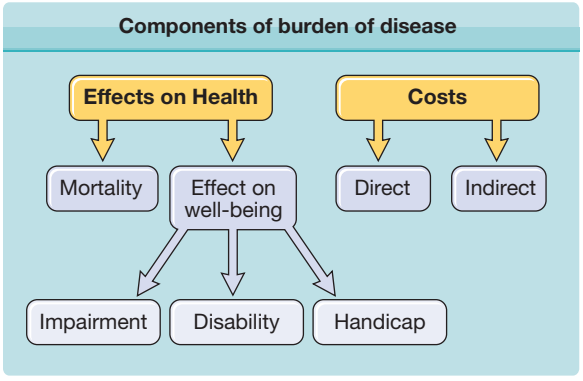

Figure 1-2 Components of burden of disease.

alization is contained in Fig. 1-2. Broadly, components of burden of skin disease are those related to effects on health or costs. Aspects of health include mortality and effects on well-being, including those related to the impairment, disability, or handicap a disease causes. For example, a patient with psoriasis may have thickening and scaling of the palms (a bodily impairment), which may cause disability (e.g., use of the hands), dysfunction (role at work), and effects on quality of life. Costs are either direct (for which funds can be paid) or indirect (for which charges are not routinely assigned, such as lost income because of disease).[31]

The measurement of burden of skin disease is challenging, in part because these conditions typically do not cause mortality and do not result in changes in easily measured laboratory tests. The most important gauges of skin disease status and progression (i.e., the physical examination and patients' reports) can be difficult to measure and compile; in most cases patients' reports of the effects of skin disease on their activities and well-being are crucial for determining the overall consequences of those diseases. The measurement challenges are heightened because people understand and value these aspects of health quite differently due to age, gender, cultural conceptions, or access to health care.

The measurement of nonfatal consequences of disease is the subject of much international scientific and political attention (http://www.who.int/healthinfo/global_burden_disease/en/, accessed Mar 5, 2010, and Chapter 3). An important point for dermatology is that patients' experiences of illness may not be adequately assessed with global measures that focus on single aspects of health, or which were developed without substantial input from patients.[32] 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.

OTHER MEASURES OF MORBIDITY: ISSUES IN QUANTIFICATION

Like all assays, measures of the nonfatal consequences of diseases must be accurate. 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. Health outcome measures also must demonstrate *responsiveness*, the ability to detect clinical change. Furthermore, even when an accurate instrument exists, the clinical significance or *interpretability* 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.[33]

CLINICAL SEVERITY OF DISEASE

A significant challenge for the development of clinimetric measures is developing a consensus among clinicians about the specific features of an individual disease that are important to include in such measures. Substantial progress in the empiric derivation of these features has been made for disease severity measures in certain skin diseases.[34,35] 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, most dermatologic severity-of-disease measures are disease-specific, and for common skin conditions, multiple instruments are often available. Among the most studied instruments to measure clinical severity of disease are the Psoriasis Area and Severity Index (PASI)[36] and the Severity Scoring of Atopic Dermatitis (SCORAD) index.[37] 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). Standardized reviews of severity measures can be helpful for informing a consensus as well as focusing futures studies; such reviews have recently been published of 20 measures of atopic dermatitis[38] and 53 measures of psoriasis.[39]

PATIENT-REPORTED OUTCOMES

As noted above, patients' reports of their experiences of disease and health care are particularly important for assessing the course of chronic diseases (like most skin diseases). Table 1-5 includes typical aspects of patients' experience that are measured in health care research.

The effects of disease on patients' quality of life can be assessed with generic instruments (which permit comparisons of effects in patients with different diseases), skin-specific instruments (which permit comparisons of patients with different skin diseases), and, more uncommonly, condition-specific instruments (which permit comparisons of patients with the same skin disease). Although more specific instruments may assess aspects of a disease that would be missed with

TABLE 1-5
Typical Instruments Used to Measure Patient Reports

Domain	Typical Instrument(s)	Comment
Overall quality of life	Medical Outcomes Study Short-Form instruments (SF-36)[40] and (SF-12)[41]	36 or 12 items; commonly used in clinical research; interpretable scores
Skin-related quality of life	Dermatology Life-Quality Index[42] Skindex-29[43], Skindex-16[44]	10 items, most commonly used, focuses on functioning 29 or 16 items, focuses on emotional effects, symptoms, and functioning
Disease-specific severity	Patient-Oriented Eczema Measure (POEM)[45], Self-Administered Psoriasis Area and Severity Index (SAPASI)[46]	Correlate well with clinician measures
Symptoms: pruritus	Itch Severity Scale[47], Pruritus-Specific Quality-of-Life Instrument[48]	Demonstrate promising measurement properties
Patient satisfaction	Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey[49]	Correlates with adherence, quality of life, and quality of care
Patient preferences	Utilities[50], Willingness to Pay[51]	Correlations among different measures of preferences can be weak

generic tools, both generic and specific tools contribute unique information to a "snapshot" of a patient's overall health-related 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. Although quality of life is the patient-reported outcome most often measured, patients' reports of symptoms, satisfaction with health care, and preferences for health states are other examples. Data continue to be accumulated about the performance of these instruments (including the use of sophisticated psychometric methods and the interpretation of their scores[52]). On a national level, to develop a core set of questions and metrics and to create item banks and repositories of items that perform well using modern analytic techniques, the National Institutes of Health has recently initiated the Patient-Reported Measurement Information System (PROMIS, http://www.nihpromis.org/).

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. However, utilities are controversial because they can be difficult to measure and can vary among patients in unpredictable ways. An increasing number of studies exist that formally measure utilities of patients with skin diseases.[50]

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. Because most skin diseases are chronic and are cared for in the outpatient setting, estimation of both their monetary and intangible costs is difficult. Costs for individual skin conditions have been calculated[53], and therapies have been evaluated in relation to their benefits and effectiveness.[54] In addition, overall direct and indirect cost to payers, patients, and society of 22 skin diseases have been reported.[55]

QUALITY OF CARE IN DERMATOLOGY

Health services research uses many 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, access to care, the processes involved in the provision of care, the particular therapeutic interventions, as well as patient and provider characteristics, are all determinants of the quality of care. Studies of both the effectiveness of care (i.e., outcomes of health care as it is usually practiced) and the efficacy of interventions (i.e., the results of interventions implemented in the idealized circumstances of a randomized clinical trial) are important. 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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Chapter 2 :: Evidence-Based Dermatology

:: Michael Bigby, Rosamaria Corona, & Moyses Szklo

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 EBM.
- 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.

WHAT IS "THE BEST EVIDENCE?"

The acceptance of evidence-based medicine (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.[7,8] 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.

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).[9] 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.[6,8] 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.[10]

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.[11,12] A meta-analysis provides an objective and quantitative summary of evidence that is

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 low-quality RCT (e.g., <80% follow-up)]	Independent blind comparison but either in nonconsecutive 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 clinical 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, accessed 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 analyses.

amenable to statistical analysis.[11] 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.[13,14] Meta-analysis has been criticized because of the discrepancies between the results of meta-analysis and those of large clinical trials.[14–17] 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.[14] The frequency of such discrepancies ranges from 10% to 23%.[14] Discrepancies can often be explained by differences in treatment protocols, heterogeneity of study populations, or changes that occur over time.[14]

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.[18,19]

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%), "lack of interest" (12%), and "sample size problems" (11%).[18] Results of studies with small samples are

less likely to be published, especially if they have negative results.[18,19] 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.[20,21] Publication bias can be detected by using a simple graphic test (funnel plot) or by several other statistical methods.[22,23] 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.

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 eTable 2-1.1 in online edition. Detailed explanations of each criterion are available.[11,24]

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 RCT.[11,24–26] Questions about diagnosis are best addressed by cohort studies.[11,24,27,28] Cohort studies, case-control studies, and postmarketing surveillance studies best address questions about harm.[11,24,29] RCT 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.[11,24]

With regard to questions about therapy and prevention, the RCT has become the gold standard for determining treatment efficacy. Thousands of RCT 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 nonrandomly selected control groups than in randomly selected control groups.[30] However, studies comparing randomized and nonrandomized clinical trials of the same interventions have reached disparate and controversial results.[30–32] Some found that observational studies reported stronger treatment effects than RCT.[30] 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 RCT on the same topic.[31,32] 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 RCT. Large, inclusive, fully blinded RCT are likely to provide the best possible evidence about effectiveness.[10,33,34]

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.[3,35,36] Nisbett and Ross extensively reviewed people's ability to draw inferences from personal experience and describe several of these pitfalls.[37] 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 preexisting knowledge structures (e.g., ideas about disease etiology and pathogenesis) and parallel failure to recognize, remember, and recall evidence that is more valid
- 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

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 Clearing-house (http://www.guideline.gov/)
- 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://www.thecochranelibrary.com/view/0/index.html). Volunteers write the systematic reviews in the Cochrane Library according to strict guidelines developed by the Cochrane Collaboration. Issue 1, 2010, of the Cochrane Library contained 6,153 completed systematic reviews. The number of reviews of dermatologic topics is steadily increasing.

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 eTables 2-1.2, 2-1.3, and 2-1.4 in online edition, respectively.[11,24] Papers that meet these criteria are more likely to provide information that is accurate and useful in the care of patients.[11,24] Critically appraising evidence consists in determining whether the results are:

- valid (i.e., they are as unbiased as possible);
- clinically important; and
- applicable 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 eTables 2-1.2, 2-1.3, and 2-1.4 in online edition, respectively.

EVIDENCE ABOUT THERAPY AND PREVENTION

Studies of therapy should randomly assign patients to treatment groups (using a table of random numbers or pseudorandom numbers generated by computer) and ensure concealed allocation (e.g., by using opaque envelopes) so that the treating physician cannot know or anticipate 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; intention-to-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 well-reported clinical trial.[35] A more complete set of criteria has been published and recently updated, and adherence to these criteria is required by many of the leading medical journals.[47,48]

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

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.[35] 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.[49] A third method, determining the impact of therapy on the quality of the patient's life, is being increasingly used in dermatologic trials.[35]

An example of the first method is commonly encountered in therapeutic trials of psoriasis. A common practice is to assign numerical values to (1) the amount of erythema, (2) the amount of scaling, (3) the degree of infiltration, and (4) the body surface area involved, and to formulate an "index" by calculating a derivative of some product of these four numbers.[50,51] 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.[50] The major problem with indices is that they confound area of involvement with severity of disease.[49] 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.[49] The second problem with indices is that they lend an air of precision to the analysis and presentation of data that is not warranted.[49] 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.[52] 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.[49]

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.[49] That is, 60% to 80% improvement is often assumed to be twice as good as 20% to 40% 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.[35,49] 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.[35,49,53] The development of scales and indices for assessing cutaneous diseases and the testing of their validity, reproducibility, and responsiveness have been inadequate.[35,49,54] 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.[49] 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.[36]

In addition to being clearly defined, outcome variables should have clinical and biologic significance.[25,26] For example, in a therapeutic trial of patients with severe acne, treatment was associated with a decrease in lesion count from a mean of 40 to a mean of 35. This numerical difference may be of statistical significance, but it does not convey the biologic significance of the change in lesion number.[49] 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 40 to 35? 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.[26,55] Examples of such endpoints include CD4/CD8 ratios instead of survival rates in studies of treatments for acquired immunodeficiency syndrome, antinuclear 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. However, surrogate endpoints must correlate with clinical outcomes 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.[11,24,41] The NNT represents the number of patients one would need to treat to achieve one additional cure or clinically relevant improvement.

The confidence interval provides a useful measure of the precision of the treatment effect.[11,24,41,56,57] The calculation and interpretation of confidence intervals have been extensively described.[58] 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.[11,24,41] 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 RCT the use of a placebo, acyclovir, prednisone, and acyclovir plus prednisone in the treatment of herpes zoster.[59] At day 30 of the trial, 48 of 52 patients 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% confidence interval for the difference in response rates is 0.35 to 0.65, and the 95% 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).[41,60] The results when the trial was repeated 10 and 1,000 times are shown in eFigs. 2-0.1A and 2-0.1B in online edition, respectively. A 95% 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% 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% 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% 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% confidence interval of the difference in response rates excludes zero difference, one can reject the null hypothesis that the two treatments are the same.[24,41,56,57]

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.[35] 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% or 50% improvement in outcome might have been missed in 57 (80%) and 34 (48%) of the studies, respectively.[61] A follow-up study conducted by Moher, Dulberg, Wells in 1994 indicated that a 25% or 50% improvement in outcome might have been missed in 84% and 64%, respectively, of 102 studies with negative results.[62] 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) 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 χ^2 testing (Yates corrected $\chi^2 = 1.35$; $p = 0.25$), 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 2,880 lives annually (based on 8,650 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.[35]

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% 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% and 20%, respectively, and the difference between them was thus 27%. The 95% confidence interval for the difference in cure rates was –10% to 51%. The upper boundary of the difference in cure rates was 51%. 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% 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% in our hypothetical example).[63] 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% (close to the observed 27%) is much more likely than a difference of –5% (far from the observed 27%).[35]

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 eTables 2-1.2–2-1.4 in online edition). 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.[35] Applying evidence to specific patients always involves physician's judgment.

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Full reference list available at www.DIGM8.com

DVD contains references and additional content

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Chapter 3 :: Global Health in Dermatology

:: Roderick J. Hay

The word "global" describing something that is worldwide is not a concept that is difficult to understand, whereas the term "health" is frequently misused on the assumption that it simply means freedom from disease. However, *health* and *disease* are not merely examples of the converse, a point that is captured by the mission statement of the World Health Organization (WHO), whose objective is to promote health. The WHO definition of health, which is widely used as the definitive descriptor of health, says that *health* is a state of complete physical, mental, and social well-being and not merely the absence of *disease* or infirmity. Therefore, global health implies a worldwide mission to promote complete well-being.

HEALTH AND GLOBAL INTERDEPENDENCE

The rational basis for this idea is simple as no nation or region is a complete island in terms of health; what affects one country may well, in time, affect another. The most obvious examples of this concept from past history involve the spread of infections. At present, there is a concerted effort to follow the international spread of HIV or avian influenza. Both present global risks to health, which is the reason why their current distributions are tracked regularly and with accuracy.[1] Spread of these diseases has occurred and will continue to occur through a combination of both social and economic factors and the movement of populations and individuals. Yet historically, infectious diseases that have spread rapidly to cause maximum chaos have often resulted from a relatively minor, and often unrecognized, episode rather than a large movement of individuals. For instance, the impact that a localized outbreak of bubonic plague had on medieval Europe when the besieged Genoese garrison in Caffa, in the Crimea, fled by ship bringing the rat host with them was not foreseen.[2] The subsequent epidemic, caused by *Yersinia pestis*, known as the Black Death, reduced the population of Europe by a third over the following 2 years. In addition to the mortality and distress, it resulted in profound social and economic changes that long outlived the epidemic itself. Predicting and tracking the international course of infections is now a key element of global surveillance.

However, global health problems and disease are not limited to infections, although the propensity to spread is more demonstrable in this group; chronic noninfectious conditions are also global. The relentless increase in the prevalence of diabetes mellitus type 2 in aging populations is such an example. Global health is affected by other factors that include the impact of social, economic, and environmental change on populations. This reflects the fact that human populations are no more isolated socially than they are geographically, but manifest a measure of interdependence where what happens in Kazakhstan may be reflected, in time, in New York City. In the case of diabetes, the causes of changes in health status are different; the international dissemination and adoption of Western dietary behaviors are, at least partly, responsible for this. Health-determining trends such as diet, lifestyles, or global warming are all examples of noninfective risk factors that may affect global health. The international spread of risks to health may follow different routes, often simultaneously.

In many parts of Europe and the United States, the decline of tuberculosis was a marker of economic progress in the twentieth century,[3] the main reduction in disease incidence, and subsequently mortality, preceding by many years the development of new specific treatments such as streptomycin or the introduction of BCG immunization. This health improvement reflected the huge social changes made during this era, such as the provision of sustainable and affordable water supplies and drainage, heating schemes, better housing, and nutrition. While the increasing prosperity and subsequent social reforms that affected the industrialized Western nations in the late nineteenth and early twentieth centuries had a huge impact, mainly for the good, in promoting better health, in international terms the benefits were relatively restricted and not global in their reach; large areas of the world did not benefit from this change. In the recent report by Michael Marmot,[4] the continuing influence of social and economic conditions on both national and global health are

clearly demonstrated and poor social and economic status linked closely to poor health indicators such as high maternal and infant mortality. He cites Sweden as an example of a country that has adopted a policy where the creation of appropriate social conditions would ensure the health of the nation. Much of this health initiative concentrates on social initiatives such as improvement of participation, economic security, and healthy working. This type of policy has been supported in both rich and poor countries. For instance, the Mexican initiative, Programa de Educacion, Salud y Alimentacion (Progresa), which provides financial incentives for families to adopt measures that will ensure social improvements leading to better health, is a good example.[5] While this may seem oversimplistic, poor health is often an indicator of social ills and vice versa; the two are interdependent. Health can make a significant impact on both micro- and macroeconomics; conversely economic performance has a direct impact on health. The WHO report on macroeconomics and health[6] asserted the view that the investment of both time and money on health improvement had multiple benefits through reduction of mortality and increase in the healthy employed, measures that would lead to improvement in both family and national economics. By ensuring good health of their populations nations would improve economic performance and social conditions, which, in turn, would improve health status of their peoples. So good health is an important facet of social and economic development, just as poor health is an indicator of poor performance in both domains. Therefore, global health becomes an important social aspiration in a world where international collaboration and interdependence as well as increasing global industry are slowly replacing, or at any rate adding another dimension to, the nation state.[7]

GLOBAL BURDEN OF DISEASE PROJECT

In order to determine the impact of global health, a consortium of international bodies such as the World Bank in 1990 commissioned a report on the global burden of disease (GBD); a project that has now gone through several iterations involving other organizations, including WHO and an international group of universities.[8] In doing this work, there were two key objectives, namely: (1) to provide up-to-date information on the incidence of disease states in all the regions of the globe and (2) to assess their impact on mortality and disability. In carrying out this work, the interdependence of health and social and economic well-being was clearly recognized. These large surveys of global disease have had to draw on the availability of studies that can provide the necessary information. A subsequent development from GBD, aimed at health in developing countries, was the Disease Control Priorities Project (DCPP), an international report focusing on sustainable measures of disease elimination or control.[9] The latest GBD round of studies is incomplete at the time of writing.[8] However, it differs from other studies in that much of the work of collecting data is the task of specialist groups, including one for dermatology. The target is to provide data covering diseases and risk factors (such as consumption of alcohol or atmospheric pollution) in the WHO designated regions and, where this is missing, to provide robust means of adducing the data using defined mathematical models. The study aims to target disease incidence at two time points—(1) 1990 and (2) 2005. It will also provide measures of mortality as well as disability. The methods used to assess the latter is more refined than previously in that lay panels (i.e., patients) will be asked to assign the weighting that determines the disability that accompanies disease states.

GLOBAL HEALTH AND THE SKIN

Within this international perspective, there is a similar connection between global health, dermatology, and the spread of skin disease. Dermatology is subject to the same factors that regulate the spread of other diseases and determine its control; infection, social, and economic factors are all important in determining the prevalence and impact of skin disease.[10] Skin infections are very common in all societies; tinea pedis (athlete's foot), onychomycosis, scabies and childhood pyoderma, viral warts, and recurrent human herpes virus (HHV1) are all examples of everyday skin infections that affect many people. There are also examples to show that this spread is mediated by human contact and, where there is facility for this to occur, for instance, in a swimming pool in the case of human papilloma virus infections of the feet and tinea pedis, there is a higher incidence of disease.[11] Likewise, movements of numbers of individuals through travel, migration, or war increase the chance of global spread of these infections. For instance, the world diffusion of infection due to *Trichophyton rubrum* is said to have followed the displacements of populations and the movement of soldiers in the 1914–1918 and 1939–1945 wars.[12] More recently, the spread of *Staphylococcus aureus* bearing the *Panton–Valentin leukocidin* (PVL) virulence gene causing furunculosis has been tracked, in some cases, to international travel.[13] Despite this, in some parts of the world there are still unique and geographically localized skin infections, largely because these occur in remote areas. The lower limb infection of children and young adults seen in remote regions of the developing world where there is a high rainfall, tropical ulcer (Fig. 3-1), is an example of a condition that has remained relatively isolated[14]; the fungal infection of the skin, tinea imbricata, is a further example.[15] However, even where there is relative isolation, changes over time such as migration can lead to epidemic spread of previously endemic disease. Tinea capitis has undergone a remarkable transformation in the Western hemisphere in the past 50 years. It has seen the introduction of an effective treatment regimen with griseofulvin initially and subsequent decline in infection rates followed by the relentless spread of one dermatophyte fungus, *Trichophyton tonsurans*, initially from a zone of endemic disease in

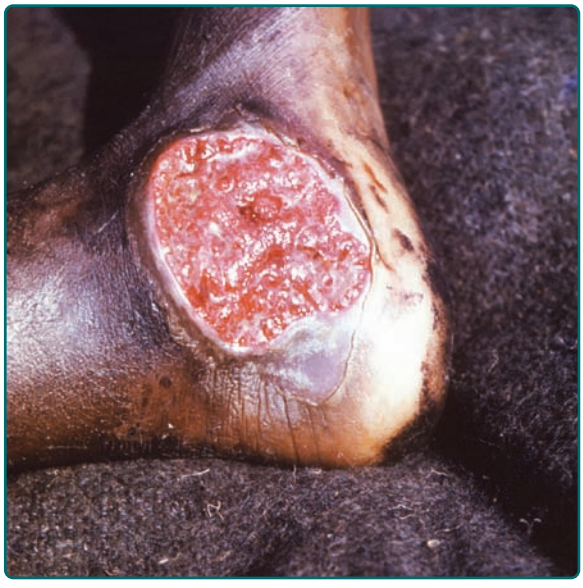

Figure 3-1 Tropical ulcer. (From CDC/K. Mae Lennon, Tulane Medical School; Clement Benjamin.)

Mexico, where it still remains as a stable infection of moderate incidence, to reach epidemic proportions in children in inner cities, initially in the United States, but subsequently in Canada, Europe, the West Indies, and Latin America.[16] The spread appears to follow an increased susceptibility to infection of children with African Caribbean hair type; in recent years it has begun to spread in Africa as well.

In a similar way, noninfectious skin disease, as with other illnesses, is also affected by those social and economic changes that are international in dimension. The complex history of the medical reaction to the fashion for sun exposure was formed initially by the recognition of the health promoting, and then health limiting, effects of sun and ultraviolet (UV) light.[17] The current concern over excessive exposure to both natural sun or UV exposure, for instance, in sunbed parlors, or as part of UV therapies, is an important stage in an exercise that started as genuine attempt at health promotion. The ancient Greeks, for instance, promoted sun exposure or heliotherapy as beneficial for a number of medical problems.[3] While largely ignored for the best part of two millennia the revolution in medical ideas in the nineteenth century led to sun exposure being adopted as a health-giving practice with the discovery of Vitamin D and the award of the Nobel Prize to Finsen for light therapy. Health-giving sun exposure was adopted widely and became a fashion that was the rage of the health conscious, delivered in spa environments such as William Kellogg's Battle Creek clinic.[18] However, the habit, perhaps fueled by the recognition that exposure to natural light was in some ways health giving, led inevitably to one of the consequences, the sun tan. It is not certain if the recognition of the suntanned skin as fashionable can all be laid at the door of Coco Chanel, who is said to have been overexposed to the sun during a holiday in Cap Antibes in France. The resulting effect on her skin color was soon to be adopted by the fashionable and white wherever they lived.[19] Soon it became a global trend in fashion. The recognition that sun exposure also led to a rising incidence of skin cancer followed more slowly, but perhaps with greater speed than that concerned with the connection between smoking and lung cancer. Protection against sun exposure has become a major global focus of preventive measures of public health medicine, from public education to the risks involved to early detection of melanoma and nonmelanoma skin cancers. Dermatological organizations have reacted with admirable speed to the recognition of the risk of UV exposure. This has been accomplished through seminars, magazine articles, public health campaigns, and training camps. The introduction of educational programs in schools has been a welcome addition.

The trend to the opposite, skin lightening, in women of color has been an equally global trend where the use of skin bleaching products has been adopted by different cultures throughout the world. The common agents in use include hydroquinone- or steroid-containing creams—with a resulting risk of the development of skin disease such as ochronosis and more general medical problems, including low birth weight infants in pregnant women using topical corticosteroids to achieve lightening.[20] As with infections, there are also examples of skin diseases that are caused by social customs or economic conditions that remain geographically localized. *Erythema ab igne* of the forearms is almost unknown in most parts of the world but is associated with the cooking of tortillas (enfermedad de las tortilleras)—so it is only seen where the tortilla is a staple of diet; oral submucous fibrosis occurs where the Betel nut is chewed is another example. However, some noninfective skin conditions occur in isolated communities for a different reason, genetic susceptibility, such as actinic dermatitis seen in native American communities in North and South America (Fig. 3-2). These are not the only examples of the relation between noninfectious skin disease as an international concern and social and economic factors. One of the earliest public health campaigns that crossed national boundaries stemmed from the recognition that industrial workers exposed to oil during the operation of large-scale spinning were

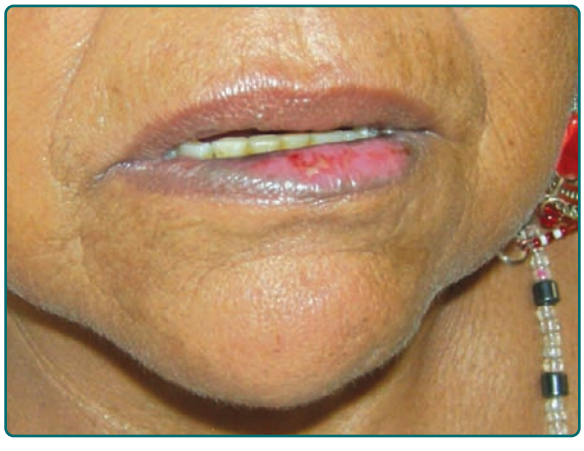

Figure 3-2 Actinic cheilitis. Mexico, Guerrero State.

susceptible to skin cancer and the ingestion of arsenic at work or as a medication was also potentially harmful through the development of skin cancer.[21] Recently, much international interest has focused on the changing face of atopic dermatitis and although the evidence suggests that this is a condition associated with societies enjoying improved socioeconomic status,[22] the quest for modifiable risks whose resolution may, in turn, provide benefit to children with this condition is now the subject of a global initiative (the ISAAC study).

So skin disease is subject to different, but nonetheless global influences, compared with other illnesses and in the pursuit of skin health there is a great need to promote international cooperation. This objective is identified, not just in order to share learning experiences, but also because the burden of skin disease is spread unequally around the world and many of the poorest nations face the greatest problems.[9] Here, the social and economic factors plus uncontrolled or poorly controlled infection play key roles in determining the pattern of disease.

SKIN DISEASE IN RESOURCE POOR ENVIRONMENTS

In the poorest countries skin disease usually ranks as one of the first three common disorders encountered in frontline medical facilities, i.e., the first point of call for a patient seeking treatment. Whereas in the developed countries many of the problems facing dermatologists and primary care practitioners are noninfectious skin diseases, the opposite is true in developing countries where infections dominate the pattern of presentation.[23] Where infections occur in the industrialized countries, the general public have widespread access to treatment through pharmacies or primary care doctors as well as specialists. Access to treatment is limited by a number of factors that range from poor training of health care workers to the need to journey considerable distances in order to obtain help.[24] Likewise in the poorest communities ready access to cash is more limited, with a large part of household economics depending on self-sufficiency in growing food or creating housing from local materials. Cash is necessary for some things such as clothing and for additional food. Treatment of even the simplest of conditions such as scabies or pyoderma presents a competing call on the available household cash income (Fig. 3-3); poor or ineffective treatment is a drain on resources that would otherwise be spent on food. The exact sums are small but their impact is large.[25]

The burden of skin disease is often unrecognized at national or international level as it is perceived to come low in the global league table of illnesses and, compared with diseases that carry a significant mortality such as HIV, community acquired pneumonias and tuberculosis, skin disease-related mortality is low. However, as skin problems are generally found to be amongst the most common presentations of diseases seen in a primary care setting in tropical[9] and nontropical[10] areas, in some regions, where transmissible diseases such as tinea imbricata or onchocerciasis are endemic, they are the commonest reason for an individual to present themselves for treatment. The GBD estimates for 2001 indicated that skin disease was associated with mortality rates of 20,000 in Sub-Saharan Africa.[8] This was comparable to mortality rates attributed to meningitis and hepatitis B, obstructed labor, and rheumatic heart disease in the same region. The disability rate calculated as disability adjusted life years (DALYs) in the same report showed an estimated total of 896,000 DALYs recorded for the region in the same year; this was comparable to that attributed to gout, endocrine disease, panic disorders, and war-related injury. While, as described before, these figures are currently being reassessed, it suggests that the burden of disease due to skin-related illness is high. Many of the international studies that have focused on the impact of illness on individuals utilize disability scores. Those interested in skin disease frequently use patient-focused measures Quality of Life (QOL) scales.[26] While these may be less objective they do, by concentrating on the impact of disease on personal values and performances, provide, according to many interested in the impact of disease, a more realistic measure of how patients are likely to use health services. Assessing the impact of skin

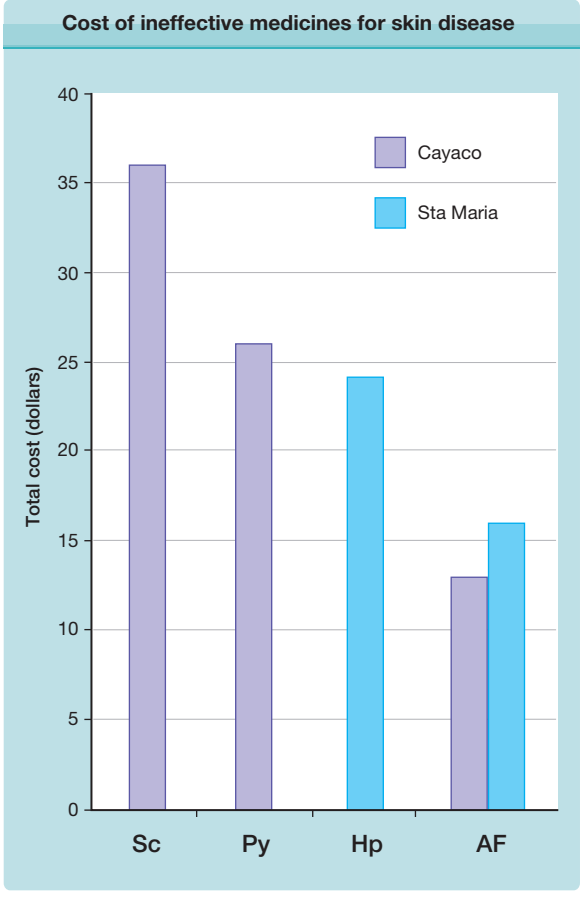

Figure 3-3 Cost of ineffective medicines for skin disease in two rural communities, Mexico. Sc = scabies; Py = pyoderma; Hp = hypopigmentation; AF = expected cost of additional food during the same period.

disease on quality of life in comparison with other chronic nondermatological diseases is difficult. However, the decline in QOL for patients with the common skin disease, acne, is similar to that experienced by patients with chronic disorders such as asthma, diabetes, and arthritis; all showed comparable deficits in objective measurements of life quality.[26] Skin disease related to HIV, which constitutes an important skin disease burden, particularly in Sub-Saharan Africa, leads to a similar diminution of QOL compared with non-HIV related skin problems, although the use of antiretroviral therapy produces a significant improvement.[27]

PRACTICAL PROBLEMS IN SKIN CARE

Despite the unequal comparison of mortality rates with other diseases, there are a number of important and relevant reasons why the needs of the populace for effective remedies or control policies for skin conditions should be in place. Firstly, the diseases are very common and patients present in very large numbers in primary care settings. In some cases more than 60% of the population has at least one skin disease.[23] Even though significant numbers never seek treatment for a variety of reasons, including lack of awareness that treatments are available, the workload generated by patients presenting with skin problems at primary care level can be huge. This is a problem in all countries but particularly in those with the lowest gross domestic product.[28] Children and the elderly, in particular, are affected, adding to the burden of disease in already vulnerable groups. Secondly, the morbidity can cause significant disability through disfigurement or restriction of movement. For instance, the effects of elephantiasis secondary to lymphatic filariasis last for years after the elimination of the filarial parasites. As stated previously, the relative economic cost of treating even trivial skin complaints in families in poor regions reduces the capacity of families to contribute to their local economies as their disposable cash is exchanged for poor medicine rather than other goods.[25] The skin is often the site where changes of a number of other neglected tropical diseases are present. Leprosy, onchocerciasis, guinea worm, HIV/AIDS, tuberculosis, yaws, and Buruli ulcer are all examples.[29] A shortage of elementary skills in the recognition and management of disease that present with skin abnormalities reduces the capacity for surveillance of these important diseases. In truth, skin disease in the tropics is a neglected problem that should be added to the list of neglected tropical diseases.

Globally, one of the current problems highlighted in a number of studies has been the management of skin disease in primary care settings. In the developing world high treatment failure rates of over 70% are common in frontline health posts.[30] The same may be true in settings in industrialized nations where lack of recognition of some skin problems at primary care level is a factor limiting effective treatment. This situation is compounded by changes to the undergraduate medical curriculum where, in many countries, the factual and academic content, such as knowledge of skin or eye disease, has been reduced to allow students to assimilate greater patient-oriented skills such as communication; the gap in learning for those not intending to follow a career in subjects, such as dermatology, yet who have some responsibility for managing skin problems, has not yet been plugged satisfactorily. One way forward in streamlining the capacity to cope with common diseases, such as skin disease, has been to prioritize treatment options. For instance, in the developing world a small number of common skin diseases, mainly infections, account for the vast majority of the disease burden. Therefore, implementation of effective treatment targeted on these conditions confers significant gains to both personal and public health. Two prime examples are scabies[31,32] and pyoderma.[33] In the industrialized nations concerted efforts to prevent or diagnose skin cancer at an early stage have formed key elements of public health strategy.[34]

IDENTIFYING RISK

In Western societies there have been few studies aimed at estimating disease prevalence or risk, a necessary prelude to health intervention. However, a study in Lambeth, South London in 1976 using a questionnaire-based population-centered approach, backed by random examination, revealed an overall 52% prevalence of skin disease of which just over half the cases were judged by the investigators to require treatment.[35] The NHANES study in the United States[36] produced very similar figures. More recent studies of skin disease burden in the United States and the United Kingdom confirm these earlier investigations. Studies from developing countries have generally been conducted through systematic community-based surveys backed by clinical examination. Published figures for skin disease prevalence in developing countries range from 20% to 80%.[9] From these studies it became clear that different populations have different levels of awareness of illness. For instance, in a study in Ethiopia between 47% and 53% of members of two rural communities claimed to have skin disease.[30] However, when they were examined 67% of those who denied having a skin problem were found to have a treatable skin condition; the majority of these were infections. Tinea capitis, which is equally common in the same population may be ignored because it is common knowledge that this follows a benign and asymptomatic course in many patients, although in those communities where the clinical form of tinea capitis, favus, occurs, the local populations recognize that this type of infection is associated with permanent scalp scarring and so present for treatment.

The main risk factors associated with skin disease in developing countries are largely socioeconomic; the most important of these appears to be household overcrowding estimated by person per room in living accommodation. For instance, in Tanzania, Gibbs found that 27% of patients had treatable skin disease in surveying two village communities; once again infections were the most common diseases found.[37] Overcrowding was a major risk factor in this latter survey. What also

seems to influence the overall prevalence and pattern of skin conditions is the existence of a number of common contagious diseases, notably scabies and pyoderma, in certain areas. Hot and humid climatic conditions may also predispose to certain skin infections such as pyoderma, thereby affecting the distribution of disease.

SKIN DISEASE—THE PATTERN AT COMMUNITY LEVEL AND INTERNATIONAL INITIATIVES

Using the World Bank figures (World Development Indicators 2002) for low-income populations in 2000, the estimated numbers of individuals infected with pyoderma and scabies based on the highest prevalence figures from community surveys in the developing world are 400 and 600 million, those based on the lowest prevalence figures are 40 and 50 million. For tinea capitis the estimated number of cases based on the highest estimates of prevalence for Sub-Saharan Africa alone is 78 million.[9]

Overall these data suggest that significant improvements could be made in reducing the burden of skin disease by focusing on the small group of conditions, particularly infections, which comprise the majority of the community caseload. This may be accomplished by community control programs (see Chapter 4). The examples of scabies and skin cancer have already been cited. There are now a number of different bodies that understand the need to prioritize and have started, at first individually but increasingly in collaboration, to try to improve this situation.

The main focus of these efforts has been the identification of the health needs for skin disease in poor countries, the simplest methods of dealing with the majority and the development of programs to cope with these. In most cases, the key elements necessary to deliver an effective program are as follows:

a. Data on skin disease and current resources that could be mobilized to deal with the problem.
b. Education of those charged with improving skin health.
c. Evidence of the efficacy of each project.

DATA ON SKIN DISEASE

Data on the global epidemiology of skin disease are inadequate, not just because current estimates of global health are subject to enormous variations. In skin disease a major and recurrent problem has been the very small number of studies that document the prevalence or incidence of disease at population level. The reasons are not difficult to identify. Firstly, because skin disease is not associated with significant mortality, the first international indicators of disease activity, death rates, have not triggered a demand at governmental or even regional levels for comprehensive epidemiological surveys. Secondly, and allied to the first point, the disability associated with skin disease is often thought to be minor—another reason why there has been few central calls for further investigation. There are also practical reasons why studies of this nature have been few until recently. Because the diagnosis of changes in the skin depends on a visual assessment, whose accuracy is largely based on experience, it becomes very difficult to teach those without the relevant experience to assign diagnostic labels. It is only comparatively recently that attempts have been made to simplify and validate diagnostic criteria for use in large population studies and those originating from the international studies of allergy now provide a global picture of the prevalence of atopic dermatitis.[38] However, this is but one example and there have been a few similar initiatives in other areas of dermatology, for example, classification of skin changes in lymphatic filariasis.[39] The upshot has been that skin disease has remained a subject where epidemiological studies have relied on the diagnosis of a trained observer, usually a dermatologist. The large studies of global disease have had to draw on the availability of a few surveys that can provide the necessary information. Most of these are the fruits of a comparatively small number of dermatologists who have taken on the task of investigating the impact of skin disease and developing measures for assessing disease prevalence and quality of life. Yet there are examples where disease presenting in the skin has attracted more global attention. Yaws, for instance, was one of the first examples of an infectious disease that was targeted by WHO for elimination through mass penicillin therapy.[40] In the first few years, the campaign made extraordinary advances with massive reductions in the numbers of new cases. As with other diseases lack of resources and major disruption, such as human conflict, have ensured that there are still pockets of yaws that have yet to be brought under control. The recognition of the risk of skin cancer has stimulated regional and national initiates in areas such as Australia[34]; but there are still few cancer registries that collect data on nonmelanoma skin cancer.

EDUCATION AND TRAINING

More effort has gone into education to improve knowledge of skin disease and its management and the examples of initiatives established by departments and national and international dermatology societies are important to recognize. These range from the national programs of skin cancer prevention to Web sites that promote public awareness. These often also include training for other health professionals, such as pharmacists, who may encounter skin disease. In the developing world the International Foundation for Dermatology has established a number of such programs.[41,42] The first of these, the Regional Dermatology Training Centre (RDTC) in Moshi, Tanzania was set up as collaboration between the International Foundation for Dermatology; The Ministry of Health and the Good Samaritan Foundation is an example of a training initiative that affects many countries. The Centre trains clinical officers with regional responsibility for skin disease, sexually transmitted infection, and leprosy, and more recently it has established an international dermatology residency-

training program for Sub-Saharan Africa. Other programs of training or assistance established in Mexico,[43] Mali,[44] Ethiopia,[45] Haiti,[46] Fiji,[47] and Cambodia amongst others are all examples of international collaboration to improve skin health in poorer countries.

HOW EFFECTIVE ARE THESE INITIATIVES?

These initiatives have been less successful in the provision of evidence that the campaigns have worked. There are some data from the sun protection programs that the incidence of advanced melanoma is improved by early screening measures.[48] However, measuring the impact of education on disease incidence is difficult, but it is clearly needed in order to justify the outlay of time and expense.

SUMMARY

In summary, the global incidence of disease affecting the skin is very large; the disability related to it is less, but is nonetheless significant. Managing this burden remains the responsibility of those specially trained in the field. Increasingly, dermatologists and dermatological nurses have turned their attention to adopting measures that benefit a wider group of individuals than the patient sitting on the other side of the consulting desk. To do so means setting up partnerships and alliances both nationally and internationally. Whether developing or assisting local or global public health schemes to control, eliminate, or improve skin problems through education or community initiatives is realistic is a matter for debate. What is certain, though, is that intervention to improve the health of those with skin problems within communities improves both the health of the people as well as the image of the profession.

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Chapter 4 :: Public Health in Dermatology

:: Hywel C. Williams, Sinéad M. Langan, & Carsten Flohr

PUBLIC HEALTH IN DERMATOLOGY AT A GLANCE

- Public health dermatology promotes skin health.
- Modern public health dermatology is still relatively underdeveloped.
- Doctors help individual patients but have little influence on the health of entire populations.
- Conversely, the impact of large population interventions is rarely appreciated by individuals.
- Prevention is often more logical than only treating sick individuals.
- A "low-risk" approach of reducing risk in the whole population for diseases such as melanoma may achieve more than a "high-risk" approach of targeting just those who have skin cancer or who are at higher 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.
- Modern public health dermatology has had some success in the reduction of skin cancer incidence and control of infectious diseases.
- Low-technology educational interventions directed at entire communities can result in more benefit than high-technology drugs targeted at a few ill individuals.

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 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]

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

As early as in the fifth century BC, Hippocrates suggested a clear link between environmental factors and disease states. In more recent centuries, the physician John Snow helped to establish the field of public health during the 1854 London cholera epidemic.[4] By carefully counting the number of deaths from cholera according to population denominators in specific London districts, he was able to establish that household water supply might be the key common factor leading to cholera deaths. Snow hypothesized that cholera was a water-borne disease, and he was able to trace the origin of the epidemic to a contaminated water pump in Broad Street, Soho. Consequently, he ordered removal of the pump handle, which was followed by a dramatic reduction in cholera deaths. Thus, Snow first made detailed planned observations, then analyzed the data, formulated a hypothesis, tested this hypothesis through experiment, and finally mounted a campaign to prevent further disease. This led to a widespread political campaigning for clean water from which millions have benefited worldwide ever since. What is intriguing about Snow's work on the causal relationship between water and cholera is that it preceded the discovery of the *Vibrio cholerae* organism by Koch a third of a century later.

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. 4-0.1 and 4-0.2 in online 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. 4-0.3 in online 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 and potential power 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, those who believe they are ill, or people 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 adverse 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 tangible and 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%.[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. 4-1). This makes sense particularly in a country like Australia, because a strong association between ultraviolet radiation and melanocytic and nonmelanocytic 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 in economically active younger people, 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]

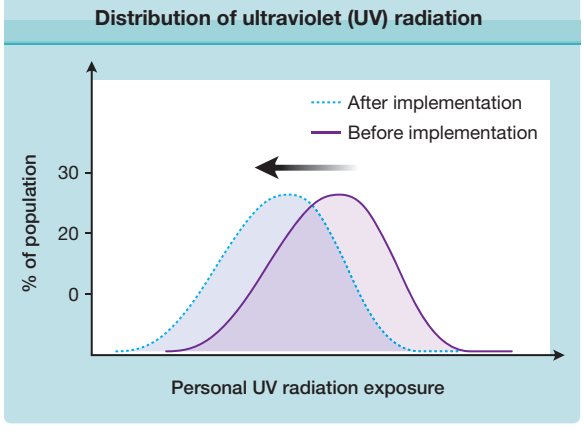

Figure 4-1 Distribution of ultraviolet (UV) radiation exposure before (*solid line*) and after (*dashed line*) implementation of a population strategy to reduce personal UV radiation exposure.

In view of the above, it seems 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. 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. Partly because of this, funding for population prevention strategies is often difficult to obtain, yet the whole population will potentially benefit, as long as such interventions are evidence based and sustainable. 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 the 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.

BALANCING BENEFIT AND HARM

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 of 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] Therefore, from a public health perspective 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% of all cases.[13] In individuals with psoriasis who smoked and who also had a family history of psoriasis, an increased body mass index might accounted for up to 48% 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 APPROACHES 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 subcellular 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% to approximately 1%. Similar dramatic decreases in scabies prevalence (from 25% to 1%) and in associated pyoderma and possibly poststreptococcal 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 (GAELF; 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 by 2020. GAELF is probably the biggest public health program ever and involves mass treatment of around 750 million people in 48 countries with antifilarial drugs and 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 increased from 42% before the training to 81% after it. Although such dramatic effects might be overestimated in a simple before-and-after study, the effects were sustained for up to 18 months after training. Paradoxically, these improvements in care were associated with a 25% 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] The principles of community dermatology in the face of mobile populations are also discussed elsewhere.[19]

Three further points in relation to public health dermatology are worth noting. The first is that although dermatologists are best placed to provide an accurate diagnosis of skin diseases, such provision may not be realistic for interventions on a public health scale in poorer countries, where there is a strong argument for embedding dermatological skills into primary health care services as has been done successfully in training health care workers in the diagnosis of leprosy in Mali.[20] The second is that public health interventions, like drug treatments, are not without their potential drawbacks. For example, limiting sun exposure in order to reduce the incidence of skin cancer may be associated with drawbacks including depression and less skin synthesis of vitamin D, deficiency of which may be associated with a range of diseases such as cancer, bone disease, and heart disease.[21] Yet recent studies of seasonal variations in vitamin D levels suggest that the commonly held view that 10 to 20 minutes sun exposure during the summer is enough to boost overall 25 hydroxy Vitamin D levels is wrong, and that sufficient sun exposure for a worthwhile benefit would be countered by an unacceptable burden of skin cancer.[22] Therefore, fortifying foods with Vitamin D seems a safer public health option than increasing sun exposure for maintaining adequate vitamin D levels.[23] Balancing benefits and harms requires special consideration in public health simply because they affect so many people. Whilst some public health interventions, such as immunization or advice on reduction of sun exposure, allow some degree of choice for individuals to heed or ignore as they choose, others, such as fluoridation of water or addition of iodine to salt, are less amenable to personal modification. Third is that 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, rather than just viewing the world of skin disease from within the narrow confines of a private practice or hospital-based practice, have already conducted population-based needs assessments for dermatologic care, followed by organization of the appropriate services at a population level. A health care needs assessment conducted in the United Kingdom found that skin diseases are one of the commonest reasons why people consult their family doctor where training was paradoxically the least.[24] New data from the World Health Organization project on the Global Burden of Diseases will include important information on the comparative burden of skin diseases compared with other skin diseases (http://www.who.int/healthinfo/global_burden_disease/en/). New methods of communication such as social networking Internet sites have become an increasingly important source of public health information.[25]

There are 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 such as infections, cancer, and atopic eczema 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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SECTION 2

Approach to Dermatologic Diagnosis

Chapter 5 :: Structure of Skin Lesions and Fundamentals of Clinical Diagnosis

:: Amit Garg, Nikki A. Levin, & Jeffrey D. Bernhard

"You see, but you do not observe"

—Holmes to Watson in "*Scandal in Bohemia*," by Arthur Conan Doyle, 1892

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 dermatological 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.

THE ART AND SCIENCE OF DERMATOLOGIC DIAGNOSIS

The diagnosis and treatment of diseases that affect the skin rest on the physician's ability to use the language of dermatology, to recognize the primary and sequential lesions of the skin, and to recognize the various patterns in which they occur. 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." 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," 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, describing and categorizing the specific lesions on the patient. Finally, one may closely examine the details of the canvas, taking in the texture and brush-strokes, 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.

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, history may be crucial. Dermatologists vary in whether they prefer to take a history prior to, during, or after performing a physical examination. In practice, many take a brief history, perform a physical examination, then undertake more detailed questioning based on the differential diagnosis that the examination suggests.

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 that the diagnosis may be immediately obvious, rendering extensive history taking unnecessary.
- 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 reevaluate the original diagnosis, monitor disease progress and complications, and modify treatment accordingly.

Box 5-1 presents a suggested approach to obtaining the history in a patient presenting with a skin problem. Clearly, not all of the questions are necessary for every patient. The physician will need to tailor the history depending on whether the chief complaint is a growth or an eruption, a nail or hair disorder, or another condition, and whether it is a new problem or a follow-up visit for an ongoing condition.

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. A guide to performing the physical examination of the patient presenting with a skin problem is presented in Box 5-2.

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

BOX 5-1 HISTORY TAKING IN DERMATOLOGIC DIAGNOSIS

CHIEF COMPLAINT AND HISTORY OF THE PRESENT ILLNESS

- ***Duration:*** When the condition was first noted and dates of any recurrences or remissions
- ***Periodicity:*** For example, constant, waxing and waning, worst at night, worst in winter
- ***Evolution:*** How the condition has spread or developed over time; often useful to ask patient whether lesion "always looked this way," or if not, how it looked when it first started
- ***Location:*** Where lesions were first noted and how they have spread, if applicable
- ***Symptoms:*** For example, pruritus, pain, bleeding, nonhealing, change of preexisting moles
- ***Severity:*** Especially for painful or pruritic conditions, it can be useful to ask patient to rate severity on a ten-point scale in order to follow severity over time
- ***Ameliorating and Exacerbating Factors:*** Relation to sun exposure, heat, cold, wind, trauma, and exposure to chemicals, topical products, plants, perfumes or metals, relation to menses or pregnancy
- Preceding illness, new medications, new topical products, or exposures
- Therapies tried, including over-the-counter or home remedies, and response to therapy
- Prior similar problems, prior diagnosis, results of biopsies or other studies performed

PAST MEDICAL HISTORY

- A history of all chronic illnesses, particularly those that may manifest in the skin, (diabetes, renal and hepatic disease, infection with HIV or hepatitis viruses, polycystic ovarian syndrome, lupus, thyroid disease) and those that are associated with skin disease (asthma, allergies)
- History of surgical procedures, including organ transplantation and bariatric surgery
- ***Immunosuppression:*** Either iatrogenic, infectious, genetic
- Pregnancies
- Psychiatric disease
- History of blistering sunburns, exposure to arsenic or ionizing radiation
- ***Medication History:*** A detailed history with particular attention to those medications started recently
- Prescription
- Over-the-counter medications
- Vitamins and dietary supplements
- Herbal remedies
- ***Allergies:*** To medications, foods, environmental antigens, and contactants
- ***Social History:*** Occupation, hobbies and leisure activities, alcohol and tobacco use, illicit drug use, sexual history (including high-risk activities for sexually transmitted diseases), dietary history, bathing habits, pets, living conditions (e.g., alone, with family, homeless, in an institution), history of travel or residence in endemic areas for infectious diseases, ethnicity, religious practices
- ***Family History:*** Of skin disease, atopy (atopic dermatitis, asthma, hay fever) or skin cancer
- ***Review of Systems:*** Constitutional symptoms (fatigue, weight loss, fever, chills, night sweats), acute illness symptoms (headache, photophobia, stiff neck, nausea, vomiting, cough, rhinorrhea, sneezing, myalgias, arthralgias), symptoms of conditions such as hypothyroidism (cold intolerance, weight gain, constipation) or psoriatic arthritis (joint pain, swelling and stiffness), which may accompany a dermatologic condition

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, and/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, and vulvar and genital areas, and when performing any procedure.
- A ruler for measuring lesions.
- Number 15 and number 11 scalpel blades for scraping and incising lesions, respectively.
- A camera for photographic documentation.
- A Wood's lamp (365 nm) for highlighting subtle pigmentary changes.

BOX 5-2 PHYSICAL EXAMINATION IN DERMATOLOGIC DIAGNOSIS

GENERAL IMPRESSION OF THE PATIENT

- Well or ill
- Obese, cachectic, or normal weight
- ***Skin Color:*** Degree of pigmentation, pallor (anemia), carotenemia, jaundice
- ***Skin Temperature:*** For example, warm, cool, and clammy
- ***Skin Surface Characteristics:*** Xerosis (dryness), seborrhea (excessive oil), turgor, hyper- or hypohidrosis (excessive or decreased sweating), and texture
- ***Degree of Photoaging:*** Lentigines, actinic purpura, rhytides

Describe the Distribution of Lesions: Localized (isolated), grouped, regional, generalized, universal, symmetrical, sun-exposed, flexural, extensor extremities, acral, intertriginous, dermatomal, follicular

PRIMARY LESIONS

- Define their type (e.g., papule, plaque, bulla)
- Describe their shape (e.g., arcuate, annular, linear)
- Describe any secondary changes (e.g., crusting, excoriations)

PALPATION

- Superficial (e.g., scaly, rough, smooth)
- Deep (e.g., firm, rubbery, mobile)

ASPECTS OF GENERAL PHYSICAL EXAMINATION THAT MAY BE HELPFUL

- Vital signs
- Abdominal examination for hepatosplenomegaly
- Pulses
- Lymph node examination (especially in cases of suspected infection and malignancy)

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 Chapter 88; these 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 Chapter 89.

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 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 von Plenck's (1738–1807) and Robert Willan's (1757–1812) work in defining basic morphologic terminology have laid the foundation for the description and comparison of fundamental lesions, thereby facilitating characterization and recognition of skin disease as, Wolff and Johnson state, 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 has been to create a universally accepted and comprehensive glossary of descriptive terms to support research, medical informatics, and patient care. Morphologic definitions in this chapter parallel and amplify those of the Dermatology Lexicon Project. Table 5-1 contains a summary of the lesions discussed.

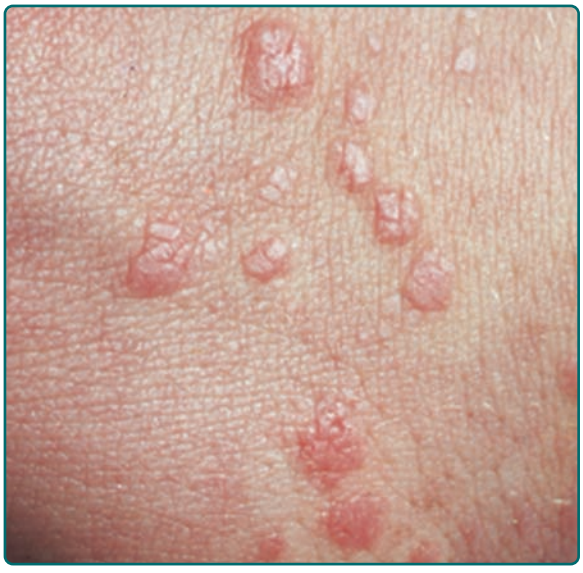

Figure 5-1 Papule. Multiple, well-defined papules of varying sizes are seen. Flat tops and glistening surface are characteristic of lichen planus.

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. 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. 5-1; see Chapter 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. Plaques are further characterized by their size, shape, color, and surface change. A clinical example is psoriasis (Fig. 5-2; see Chapter 18).

NODULE. A nodule is a solid, round or ellipsoidal, palpable lesion that has a diameter larger than 0.5 cm. However, size 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. 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. 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 of a nodule is nodular basal cell carcinoma (Fig. 5-3; see Chapter 115).

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.

CYST. A cyst is an encapsulated cavity or sac lined with a true epithelium that contains fluid or semi-

TABLE 5-1
The Lesions of the Skin

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					

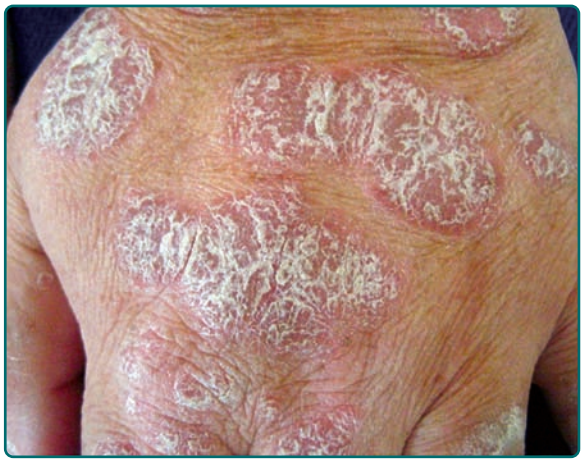

Figure 5-2 Plaque. Well-demarcated pink plaques with a silvery scale representing psoriasis vulgaris.

solid 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. Depending on the nature of the contents, cysts may be hard, doughy, or fluctuant. A clinical example is a cystic hidradenoma (Fig. 5-4; see Chapter 119).

WHEAL. A wheal is a swelling of the skin that is characteristically evanescent, disappearing within hours. These lesions, also known as *hives* or *urticaria*, are the result of edema produced by the escape of plasma through vessel walls in the upper portion of the dermis. Wheals may be tiny papules or giant plaques, and they may take the form of various shapes (round, oval, serpiginous, or annular), often in the same patient. Borders of a wheal, although sharp, are not stable and in fact move from involved to adjacent uninvolved areas over a period of hours. The flare, or ring of pink erythema, of a wheal may be intense if superficial vessels are dilated. If the amount of edema is sufficient to compress superficial vessels, wheals may in fact be white in the center or around the periphery, producing a zone of pallor. With associated inflammatory disruption of the vessels walls, wheals may have a deeper red color, may be purpuric, and are more persistent.

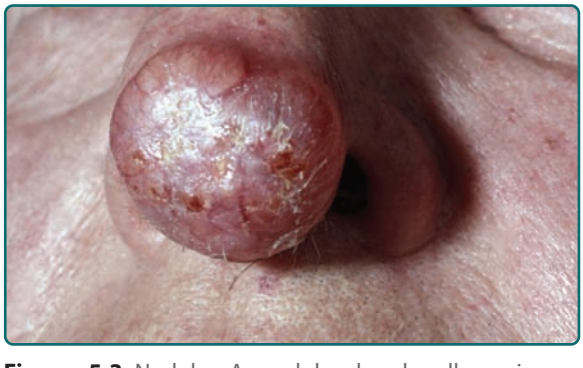

Figure 5-3 Nodule. A nodular basal cell carcinoma with well-defined, firm nodule with a glistening surface through which telangiectasia can be seen.

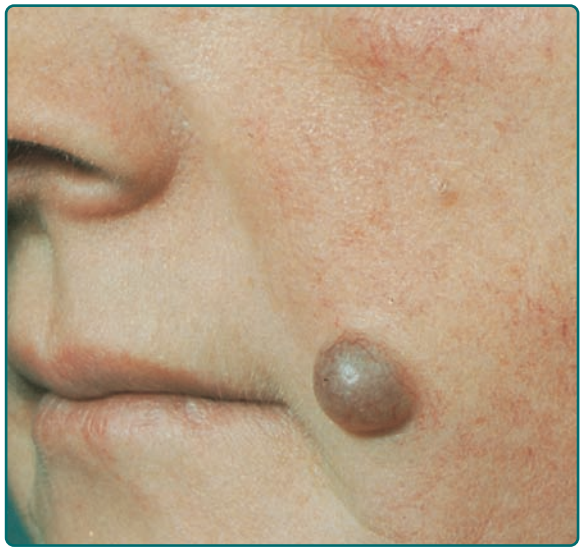

Figure 5-4 Cyst. A bluish colored resilient cyst filled with a mucous-like material on the cheek is cystic hidradenoma.

A clinical example is dermatographism (Fig. 5-5; see Chapter 38).

Angioedema is a deeper, edematous reaction that occurs in areas with very loose dermis and subcutaneous tissue such as the lip, eyelid, or scrotum. It may occur on the hands and feet as well, and result in grotesque deformity.

SCAR. A scar arises from proliferation of fibrous tissue that replaces previously normal collagen after a wound or ulceration breaches the reticular dermis. Scars have a deeper pink to red color early on before becoming hypo- or hyperpigmented. In most scars, the epidermis is thinned and imparts a wrinkled appearance at the surface. Adnexal structures, such as hair

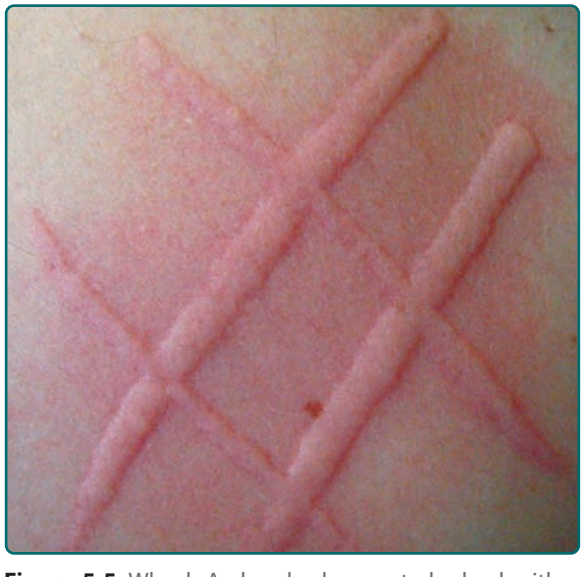

Figure 5-5 Wheal. A sharply demarcated wheal with a surrounding erythematous flare occurring within seconds of the skin being stroked.