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Editorial

Online Medical Education and Consultation for the Dermatologist

It is amazing how much we have changed over the last decade. Digital technology has changed the world in profound and exciting ways. Today we can communicate instantly with our colleagues without worrying about traditional limitations of time and location. Ten years ago, the PC was just beginning to achieve broad acceptance. Today, the PC and the Internet have all reached critical mass, creating opportunities and connections for hundreds of millions of people around the globe.

But these changes are just the beginning. As more and more of the world's information and communication moves to digital form, it will open to a new world of connected experiences that link our interests and our communities[1]. This has created the unprecedented opportunities that the provider and the recipient need no longer be physically present in the same place. A remote dermatologist can utilize the digital technology and the internet for his own continuing medical education.

The WHO Telematics Policy has stated that with regard to its health-for-all strategy it recommends "….integrate the appropriate use of health telematics in the overall policy and strategy for attainment of health for all in the 21st century, thus fulfilling the vision of the world in which the benefits of science, technology and public health development are made equitably available to all people everywhere."[2]

The word "tele" derives from a Greek word meaning "at a distance". Hence telemedicine is the delivery of health care and the exchange of health care information across distances.[3] It includes rapid access to shared and remote medical expertise by means of telecommunication and information technologies no matter where the patient or the relevant information is located. It is not a new branch of medicine. In fact telemedicine has existed centuries years ago when information about Bubonic plague transmitted across Europe by such means as bonfires.

The recent advent of low cost high megapixel digital cameras combined with improved high speed broadband internet access has allowed teledermatology to become a reality. In clinical trials, store-and-forward teledermatology consultations produce similar clinical outcomes when compared with conventional clinic-based consultations.[4] In this study, the authors compared the clinical outcomes of store-and-forward teledermatology with those following conventional clinic-based consultation. In the usual care group, 65% were rated as 'improved', 32% as 'no change' and 3% as 'worse'. For teledermatology group, 64% were rated as 'improved', 33% as 'no change' and 4% as 'worse'. One can communicate with colleagues over the face of the globe and benefit in many ways. This has open up avenues for communication across the continents at the speed of a click. The ability to share cases electronically is a great teaching and learning experiences. We can now consult our peers around the world.[5]

While the traditional method of learning still holds true, advances in global mass communication allow one to keep in touch with far-flung colleagues and interactively share our patient's problems and occasionally allowing one to solve difficult diagnostic and therapeutic cases through a virtual grand rounds in dermatology (VGRD)[6]. These colleagues could be as far north as Canada to as far south as New Zealand. They could be experts in areas of dermatologic subspecialty such as dermatopathology, pediatric dermatology, immunodermatology, infectious dermatology, intensive care dermatology, and dermatologic surgery. This was conceived of as a collegial meeting ground for dermatologists who might not have the luxury of being associated with a medical center or for those academics who are willing to share their expertise with far-flung cyber-colleagues. It is a place where difficult patients can be presented for help with diagnosis and treatment. VGRD (and the more recently created Anak-VGRD) are vehicles to help the orphan patient. The Shelleys in their 1988 letter to the NEJM define the orphan patient as an individual "with a unique, inchoate, baffling and often disabling disease and yet clearly not discernable in the medical literature."[7] Their case histories can be presented on either of these sites and they may benefit from the opinions of many seasoned dermatologists from around the world.[8]

There are a small but increasing number of publications on the subject of teledermatology. A Pubmed search on the keyword "teledermatology" at the title field listed 203 papers. The first paper was published in 1995. There are 61 papers published since January 2005. There are many dermatological internet resources. Among the most popular ones are Pubmed (http://www.ncbi.nlm.nih.gov/sites/entrez), Google (www.google.com), New Zealand Dermnet (www.dermnetnz.org), Cochrane Skin Group (http://www.nottingham.ac.uk/~muzd/), ebDerm.org (http://www.ebderm.org/), Dermatology Online Journal (http://dermatology.cdlib.org/) and International Journal of Dermatology (http://www.blackwellpublishing.com/journal.asp?ref=0011-9059).

Many useful atlases are also available such as Global Skin Atlas (http://www.globalskinatlas.com), Dermatologic Image Online Atlas (http://www.dermis.net/index_e.html) and Dermatology Image Atlas (http://dermatlas.med.jhmi.edu/derm/)

Case Histories can be assessed online at virtual grand rounds in dermatology (www.vgrd.org), New York University Department of Dermatology Tuesday Evening Clinical Conference (http://www.med.nyu.edu/dermatology/sem_conf/tuesdaynight.html) and Australian's Dermconsult (http://www.dermconsult.com.au/index.cfm).

There is indeed a need for world-wide consultation for problem patients who have been told repeatedly "There is nothing more that can be done for you." In the past when we began practice such difficult patients were sent to university centers where the teaching staff would pool their experiences and medical officers would scan the Index Medicus and text books for help. Today, the difficult orphan patient can have many wonderful adoptive dermatologist parents. One can go to one's computer and adopt one of these orphan patients from the virtual grand rounds in dermatology (www.vgrd.org)[9]. This will make both the dermatologist and the patient happier.

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Review

The Role of Dermatopathology in the Practice of Dermatology

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Abstract
Dermatopathology is one of the most powerful diagnostic tools in clinical dermatology. In this diagnostic process, the dermatologist and the dermatopathologist are a team in patient care, where the dermatologist must know when biopsies are indicated; be able to select lesions to biopsy those that are likely to yield diagnostic results; skillfully procure the biopsy samples; and provide the dermatopathologist with an accurate history, clinical description, and clinical differential diagnosis. On the other side, the dermatopathologist should be readily accessible to the clinician, and be dogged in the pursuit of an accurate histological description and clinically relevant diagnosis. In this article, we will discuss the finer points of skin biopsy, benefits and limitations of biopsy interpretation, and the future potential of skin biopsy in the selection of targeted therapy and individualized patient care.

Keywords
Biopsy; shave; punch; excision; diagnosis; accuracy; targeted therapy

Introduction

Dermatopathology, a sub-specialty of anatomic pathology and dermatology, is the study of skin disease, which encompasses both the diagnosis of individual patients via evaluation of skin biopsies, and the study of the etiology and pathogenesis of skin diseases at the tissue, cellular and molecular levels[1-6]. Dermatopathologists work in close association with dermatologists (some dermatologists are both, and read their own slides).

In the United States of America, certification in Dermatopathology requires the completion of 4 years residency training in either dermatology (internship plus 3 years of dermatology) or anatomic pathology. Following that, an additional one to two years of dermatopathology fellowship training is completed. For pathology trainees, this training includes 6 months of clinical dermatology, and for dermatology trainees, 6 months of anatomic pathology training. The final step for qualification is to obtain board certification in Dermatopathology, which is jointly sponsored by the American Boards of Pathology and Dermatology. Outside of the USA since 2003, the International Board of Dermatopathology has certified qualified candidates from countries other than the United States by a test given in Europe[7]. The International Board of Dermatopathology seeks to improve the standards of dermatopathology as well as the quality and number of dermatopathologists around the world.

In dermatology, clinical diagnosis is based on gross morphologic findings-type of individual lesion (e.g. macule vs. papule), the configuration of these lesions (e.g., grouped, linear, annular), their distribution (e.g., localized, dermatomal, generalized), and duration of disease. The accuracy of clinical dermatologic diagnosis varies greatly and is dependent of expertise and experience, varying from 26%-34% for family physicians to 71-75% for dermatologists assessing neoplastic and inflammatory skin disease respectively[8]. This may be in part due to lack of logical and reliable systematic method for clinical dermatologic diagnosis[9]. In contrast, dermatopathologic diagnoses can be arrived at by application of a logical algorithmic method that utilizes precise, repeatable criteria[1, 10]. Therefore, skin biopsy enhances clinical evaluation allowing for definitive diagnosis and the ruling out of other specific diagnoses or categories of skin disease. Furthermore, accurate diagnosis is the first step in effective treatment, thus, integral to the process of disease management.

As advances in immunopathology and molecular pathology increase the understanding of causes, mechanisms, and consequences of skin disease, there is the expectation that these advances will allow for more precise management and potentially, personalized (targeted) therapy of skin disease[11]. Dermatopathology plays, and will play, a crucial role in these endeavors.

In this article, we will review the finer points of skin biopsy, benefits and limitations of biopsy interpretation, and the future potential of skin biopsy in the selection of targeted therapy and individualized patient care.

The biopsy

As clinical diagnosis is not 100% accurate[8], other diagnostic tests are employed in dermatology, including skin scrapings, dermatophyte culture, trichograms, serologic tests, and skin biopsy to aid in accurate diagnosis. Skin biopsy is one of the most powerful diagnostic tools in the armature of dermatology. Although mostly used for routine light microscopy, skin biopsy specimens can be utilized for microbiologic, immunopathologic, cytogenetic, and molecular analysis, often utilizing the same formalin fixed, paraffin embedded specimen as for light microscopy. The indications for skin biopsy are many, but not absolute[12]. The following are some helpful guidelines for when to biopsy:

- Suspected skin cancer
- Dermatoses not responding to rational therapy
- Cutaneous manifestations of systemic disease
- Persistent ulcers (to rule out neoplasia or infection)
- For diagnosis confirmation, when potential therapy has serious adverse affects, is expensive, and/or is labour (time) intensive
- When dermatopathology is the only definitive way to render a specific diagnosis (e.g. bullous dermatoses)
- When specific infectious agents are suspected that are slow growing or difficult to culture
- Unusual or atypical dermatologic presentations

There also exist scenarios in which biopsy will not be helpful such as in chronic pruritic dermatoses like atopic dermatitis where the dominant pathology will be the consequence of 'human finger nail disease': lichen simplex chronicus, excoriations, scars and ulcerations. Lastly, skin biopsy should never replace clinical acumen. The clinical presentation and diagnostic impression should be the guide to biopsy selection; moreover, this clinical data is requisite for accurate dermatopathologic diagnosis, particularly inflammatory skin disease[13].

Site and lesion selection

Cutaneous biopsy is not simply removal a sample of skin and/or subcutis, but a sequential process of essential steps that if performed correctly can lead to specific diagnosis or at least, assignment to a categorical group of diseases, narrowing the differential diagnosis and excluding other, specific disorders[1, 14, 15]. **See table 1.**

The age of the lesion and location of the biopsy are critical for maximizing diagnostic yield[1, 14, 15]. Clinical judgment comes to the forefront because different pathologic processes are best identified at different stages of their development and at different locations. In general, active lesions are ideal for diagnosing inflammatory disease. Early-mature lesions, which have not been manipulated or secondarily infected, are to be sought foremost. These typically take the form of macules, papules or vesicles. Pruritic primary lesions will almost invariably be scratched producing erosions, ulceration and crusts. Breakdown of the skin barrier also results in secondary bacterial and fungal infection, which also obscures the primary disease process, confounding the dermatopathologist. In the diagnosis of vesiculobullous disorders, early evolving lesions (i.e. an edematous papule rather than a fully developed blister whose roof will be lost during biopsy, are preferred). Old lesions of subepidermal bullous disorders can appear to be intradermal vesicles following regeneration of a new epidermis. In cases where there is no evidence of a primary lesion, biopsy can be helpful in verifying that there is not an authentic primary process, particularly if dermatitis artifacta is suspected. For ulcerative and blistering diseases, sampling should be focused at the edge, to include both the margin of the blister or ulcer and the surrounding "normal" skin. This transition area holds the greatest potential of leading to the correct diagnosis. Another important technique is to sample multiple sites, and especially lesions at different stages in development. This may be crucial as some diseases mirror one another during the early phases (e.g., pityriasis lichenoides et varioliformis acuta and erythema multiforme[16]) whereas many others may all come to resemble "burned out" lesions. In short, a biopsy is a snapshot in time that records a truth only in part, that is one time interval of an evolutionary process. Multiple biopsies from different stages of lesional tissue in effect produces 'time lapse footage' allowing for more accurate diagnosis[1].

Varying anatomic locations also play an important role for the clinician's approach to biopsy[1, 14, 15]. For example, when a rash is present on the legs above and below the knees, more proximal lesions should be sampled preferentially due to the morphologic distorting effects of stasis and the resultant increased difficulty of healing. Biopsy of inflammatory disorders affecting elbow and knee should also be avoided due the co-existence of lichen simplex chronicus at these sites. Shave biopsies are preferred over punch and excision when sampling superficial lesions from the back and shin due to the thickness of the back dermis (may exceed 1cm) and taught nature of shin, respectively. These characteristics increase the risk of hematoma, dehiscence, infection and hypertrophic scarring/keloid formation in these regions from deep punch or excisional biopsy. When approaching lesions on the hands and feet, punch biopsies are best avoided when possible due to the proximity of myriad crucial structures (large vessels, tendons, nerves and bones). Large and deep shave biopsies should arouse concern when sampling lesions from the chest and buttocks due to the risk of hypertrophic scarring/keloid formation in these potentially cosmetically important areas. Shave biopsies are preferred over punch biopsies, however, for lesions on the scalp due to its tight, thick and vascular nature. In addition, there is little or no risk of resulting alopecia because of the superficial nature of shaves. However, if the cause of alopecia is being sought, a 4mm punch biopsy(s) extending

Table 1. Essential steps in skin biopsy before dermatopathologic evaluation

Steps	Practical Points
Selection of one or more lesions to be sampled	• Well-formed, mature lesion is optimal • Early lesion is preferable in bullous disorders *Older subepidermal blisters often may appear to be intraepidermal due to reepithelization* • Excoriated, scarred, and/or traumatized lesions should be avoided • Multiple biopsies may be necessary in generalized eruptions as lesions may be at different stages of evolution • For immunofluorescent studies for bullous dermatoses, peri-lesional tissue will give optimal results • Adjacent normal tissue are helpful in disorders of pigmentation, sclerosing disorders/atrophoderma, anetoderma, and connective tissue nevi
Removal of the sample by the biopsy method that is optimal for diagnosis	Punch biopsy: • Inflammatory disorders • Alopecia • Dermal lesions Shave biopsy: • Lesions confined to the epidermis Excisional biopsy • Ideal for melanoma and other smaller lesions of suspected skin cancer Incisional biopsy • In case of large lesions where primary closure is difficult • To confirm diagnosis and avoid unnecessary surgery • Panniculitis
Delicate handling of the specimen	• Avoid crush artifact by avoiding forceps and using needle to lift punch biopsy specimen • Avoid specimen dry-out by placing immediately in fixative or covering with saline-soaked guaze
Proper fixation of the specimen	Buffered Formalin (fixative should be at least 10x volume of lesion): • Light microscopy • Immunohistochemistry, in situ hybridization, PCR Michel's or Zeus' transport medium • Direct immunofluorescent studies Glutaraldehyde or modified Millonig's fixative: • Electron microscopy
Reporting of clinical information	The importance of answering every question of laboratory requisition cannot be over emphasized • Demographics: name, age, sex, race, address, pertinent medications and medical history • Description: morphology of individual lesions and their, configuration and number • Duration of lesions • Diameter, site of biopsy, and/or distribution of lesions • Diagnosis: report most likely clinical diagnosis and differential diagnoses • Report use of topical and/or systemic therapy • Any relevant previous biopsies must noted

to the subcutis is preferred, and is to be sectioned transversely/horizontally by the pathology lab for optimal histologic assessment of hair growth[17, 18]. Shave biopsies (or smaller punches, <3mm) are also preferred over punches near the eyelids, ears, nose and lips. This is due to the cosmetic concerns of dog ears. In particular, eyelid biopsies should avoid the conjunctival margin, and attention must be given to insure that the vermilion border is aligned after lip biopsy.

Choice of biopsy procedure

Skin biopsies may be generally categorized into 3 types: shave, punch, or excisional[15]. Incisional, curettage and snip biopsies are other techniques. Selection of biopsy procedure is paramount in its influence on diagnostic yield, cosmetic result and procedural time requirement. Each of the three offers their respective advantages and limitations, which vary based upon the clinically suspected nature of the lesion to be sampled. (**See table 1**). Therefore, it is the clinical suspicion of the pathologic process, based upon the gross morphology of the lesion and its location, which determines the best technique for sampling lesional tissue.

Shave biopsies are often optimal for evaluating lesions restricted to the epidermis (superficial benign & malignant tumors - e.g., seborrheic keratoses, dome shaped nevi, & non-melanoma malignancies like superficial basal cell carcinoma). Advantages include minimal bleeding, rapid healing (because only a superficial wound is created), minimal scarring and therefore desirable cosmetic results, ability to remove wider lesions, and the relative speed and ease of the procedure. These advantages may become particularly desirable when evaluating difficult anatomic sites to suture such as the shin and back. The primary limitation of a shave biopsy, similar to its advantages, arises from its implicitly superficial nature. Dermis and subcutis are rarely included, and pathologic processes therein may be missed. In addition, future punch and excisional biopsies at the same site may be confounded by a preceding deep shave, due to indentation and subsequent scar formation[1, 14, 15].

Punch biopsies are typically ideal for inflammatory or infiltrative diseases in which the predominant pathology lies in the dermis (most superficial inflammatory and bullous diseases; diffuse and nodular infiltrates; benign & malignant tumors, except melanoma). Advantages over shave biopsies lie primarily in the increased depth. When properly performed, punch biopsies include the epidermis, dermis and subcutaneous fat. The standard punch biopsy is 4mm in diameter, but their size can vary from 1mm diameter up to 8mm, which can sometimes be substituted for elliptical, excisional biopsies of larger lesions. Although similarly simple to perform as a shave, they require a bit more time and equipment, and typically result in increased scarring. However, small punches (~2mm) may have excellent cosmetic results when care is taken to produce a defect falling within skin tension lines, making them surprisingly ideal for facial biopsies[1, 14, 15].

Excisional biopsies are the technique of choice for lesions with a high index of suspicion for cancer, and those that require removal. The former refers primarily to potential melanomas, and the latter may include subcutaneous cysts, lipomas and those too large for punch biopsies (i.e. >8mm). In addition, deep inflammatory processes such as nodules of erythema nodosum may benefit from this technique. The advantage lies in increased depth and area, however at the cost of increased scarring, and increased time and skill to close the wider defects. Excisional and incisional biopsies are also employed to acquire specimens, which include both lesional and adjacent normal skin, to evaluate subtle connective tissue changes[1, 14, 15]. ***Incisional biopsies*** are also used in the case of large lesions where primary closure is difficult, to confirm diagnosis, and to avoid unnecessary surgery, and for sampling subcutaneous disorders like panniculitis.

Curettage specimens from the skin are the least desirable, and some feel that it is best to never send them to pathology at all[14]. This is due to the high likelihood of losing fragments and the difficulty of reconstructing anatomic orientation on histologic sections. In cases clinically requiring curettage, it is best to send an intact shave biopsy prior to curettage and desiccation of the lesion site. ***Snip (scissor) biopsy*** is a useful procedure for sampling and excising polypoid and filamentous lesions with a small base.

Biopsy to confirm diagnosis of suspected vasculitis provides a useful model for how to approach the type, timing and site of skin biopsy[19, 20]. Firstly, the optimal time for skin biopsy is 24-48hrs after the appearance of a vasculitic lesion. If the biopsy is poorly timed, the pathologic features of vasculitis may be absent- a fact that clinicians must bear in mind when interpreting a negative biopsy from a patient whose clinical findings suggest vasculitis. **See figure 1**. A punch biopsy of a lesion at the appropriate stage ("lesions have life-spans" and therapy affects the histopathologic findings) will enable histologic confirmation of most small-vessel vasculitides. Purpuric lesions obtained in the first 24hours are characterized by fibrin deposits within the vessel wall accompanied by neutrophilic infiltration and surrounding hemorrhage and nuclear debris. After 24 hours, neutrophils are replaced by lymphocytes and macrophages. Biopsy of lesions greater than 48hrs old, regardless of the underlying form of vasculitis, may show lymphocyte-rich infiltrates. Secondly, choice of a shave biopsy, punch biopsy or excisional biopsy will affect which vessels are examined as the type of vessel is dependent on location within the skin and subcutis- i.e. the deeper the location, the larger the vessel. Thus, if a medium vessel vasculitis such as polyarteritis nodosa (PAN) is suspected, the biopsy must include the subcutaneous fat where medium sized vessels are situated. Incisional biopsy is required for cases affecting larger vessels (nodular vasculitis and giant cell arteritis). In the case of livedo reticularis/racemosa, a deep biopsy extending to the subcutis should be taken from the center of the circular livedo segment (the 'white' center, not the 'red'

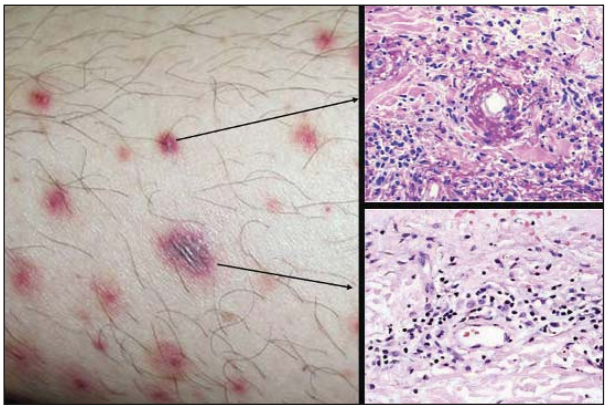

Fig 1. Biopsy is required to confirm the clinical suspicion of cutaneous vasculitis when a patient presents with palapable purpura of the lower extremeties. Choosing an early lesion, less than 48hours, is crucial in identifying the diagnostic histologic changes of vasculitis- neutrophilic infiltrate disrupting a small vessel associated with nuclear debris (leukocytoclastia) and fibrin depositis (top right). After 48hours, fibrin is lost and lymphocytes and macrophages replace the neutrophilic infiltrate (bottom right).

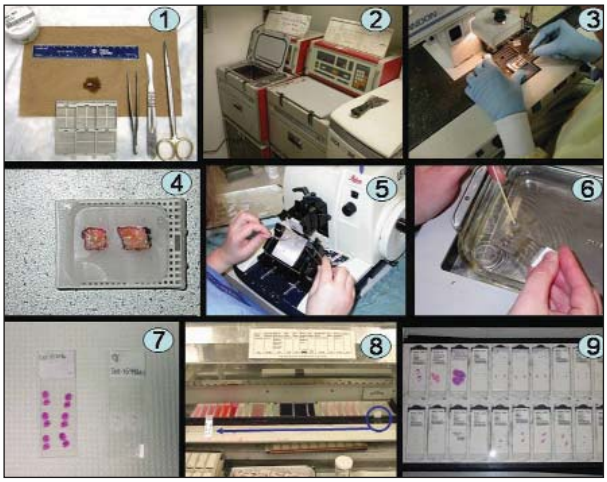

Fig 3. Laboratory processing of the biopsy specimen for histologic assessment- from fixed tissue to hematoxylan and eosin (HE) stained tissue section. 1) All specimens are signed a unique accession number, and are "grossed" or "cut in". This process entails describing the type of specimen, its dimensions, and any other distinguishing characteristics (in this case, a small, orientated ellipse of skin). The tissue is then sectioned and submitted in tissue processing cassettes labeled with the accession number and block number. 2). The tissue cassettes then undergo automatic processing to further fixate the tissue, dehydrate the specimen, and impregnate with paraffin wax. 3) Processed tissue sections are then embedded in wax. 4) Paraffin block with embedded tissue. 5) Paraffin blocks are then trimmed and 5µ sections are cut from them. 6) These 5µ tissue sections are floated in water bath and then placed on slide with the specimen's unique accession number and block numbers from which they were cut from. 7-8) Unstained sections are then stained with HE (in this case by an automatic stainer (8)). 9) The HE stained slides are then cover-slipped and placed in slide trays with the submitting requisition for microscopic assessment. The histologic description and diagnosis are then transcribed onto a report with the patients demographic data, its pathologic accession number, and the gross description. "Sign out", signing the pathology report is the last step of the process before the report is distributed to the referring clinician.

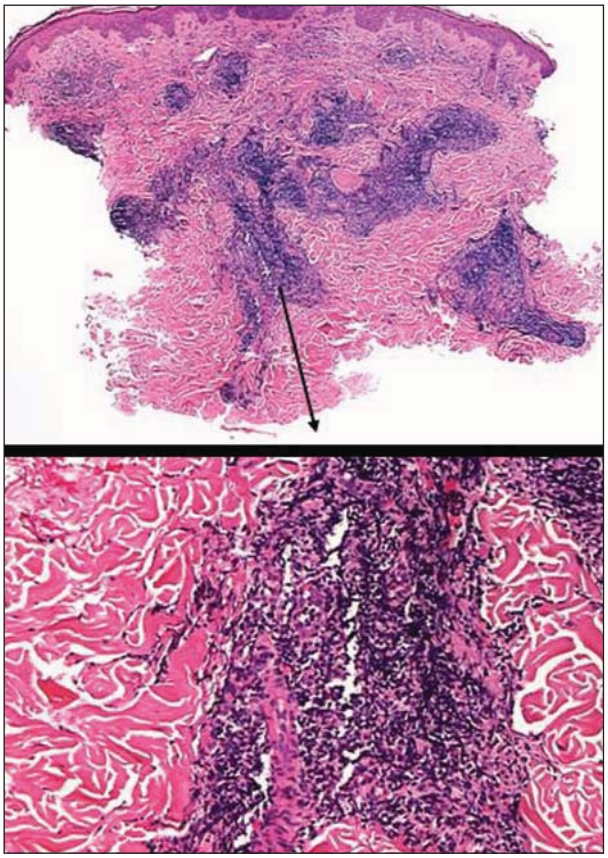

Fig 2. Crush artifact-a mild example. Squeezing the specimen with non-toothed forceps causes crush artifact. In this punch biopsy of cutaneous lymphoid hyperplasia, note the dark, smeared appearance of the infiltrate in lower dermis (top panel) due to compression and distortion of the inflammatory infiltrate (bottom panel). If crush artifact is severe, the biopsy specimen will be unreadable. Inserting a needle into the dermis or gently using a toothed forceps to lift the tissue out of the punch defect helps avoid crush artifact.

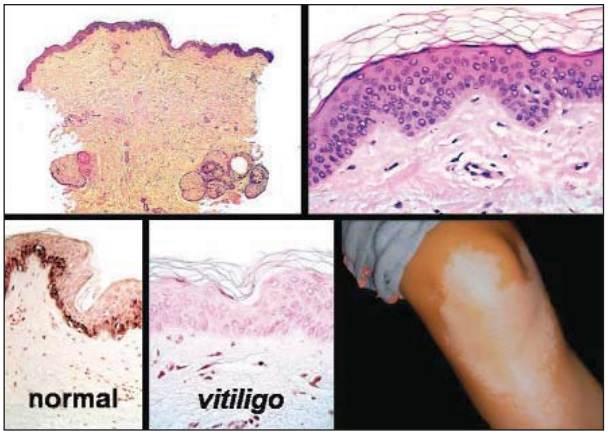

Fig 4. Vitiligo (bottom right panel) is one condition that can resemble normal skin under the microscope (top left and right panels). Unless the consulting physician informs the dermatopathologist that he suspects and wishes to confirm the diagnosis of vitiligo, the dermatopathologist could interpret this biopsy specimen as normal, "unremarkable" skin. Fontana-Masson stain demonstrates the absence of melanin vitiligo skin (bottom left panels).

periphery) because this where the stenosed vessel responsible for the cyanotic periphery is located. Thirdly, biopsies should be obtained from non-ulcerated sites, or if not possible, from the edge of an ulcer. Lastly, omission of a biopsy for direct immunofluorescence (DIF) studies wastes an opportunity to collect potentially valuable information and often leads to misdiagnosis. For example, DIF provides the only way of diagnosing Henoch-Schonlein purpura (IgA vasculitis). It is best to take 2 biopsies, one for light microscopy and one for DIF examination, rather than split one specimen. Procuring multiple biopsies and extending the biopsy depth to the subcutis and fascia can significantly increase the diagnostic yield for vasculitis[19]. If multiple biopsies do not reveal evidence of vasculitis, then a pseudovasculitis (hemorrhagic or vaso-occlusive) disorder should be strongly considered[20].

Proper fixation and optimal preparation (Laboratory handling)

Proper fixation of biopsy specimens is a crucial part of the biopsy procedure and requires at least a superficial understanding of the various available pathologic studies. For standard hematoxylin and eosin histology, specimens should be placed immediately in a container of 10% neutral buffered formalin, and the volume of fixative should be at least 10 times the volume of the specimen. Be sure the specimen is completely submerged, and avoid "drying out" between the biopsy procedure and being placed into fixative. If the specimen is to be transported through cold weather, check with the laboratory to ensure that the fixative contains antifreeze. Also, when handling specimens, take special care to avoid excessive squeezing and physical trauma (e.g., pressure from forceps or a dull surgical blade). Freezing, drying and crushing may cause significant morphologic artifacts, thus limiting histologic interpretation, and possibly precluding definitive diagnosis. **See figure 2**. Histochemical, immunohistochemical, and chromogenic or fluorescent in situ hybridization studies may also be performed on standard formalin fixed, paraffin-embedded tissue cassettes. In addition, DNA can be readily extracted from these samples for molecular testing for infectious agents, or genetic aberrations such as mutations, monoclonal gene rearrangements, promoter methylation, and gene amplifications. For specimens requiring direct immunofluorescence (DIF), formalin must be strictly avoided; instead the tissue should be transported in saline (to avoid drying) or fixed in Michel's transport medium. Specimens for microbiology (culture and sensitivity) should be kept fresh and as sterile as possible. For cytogenetic analysis/karyotyping, the tissue should be submitted fresh or in normal saline. Electron microscopy requires tissue to be transported in glutaraldehyde or Millagong's fixative.

At the pathology laboratory, the patient's name is verified and the specimen is assigned a unique accession number, which is noted on the requisition form and on the specimen container. Specimens are routed to a 'grossing' area, where a technician is responsible for orienting and properly dissecting specimens. Most routine punch and shave biopsies are bisected vertically (epidermis to subcutis) and the halves submitted for processing (fixation, dehydration, and wax impregnation) and embedding in paraffin wax blocks. Larger specimens are serially sectioned, and if performed for cancer, the margins are inked to aid in histologic assessment of margin involvement. If the specimen is oriented (specific margins are identified), its margins are differentially inked and sections are submitted with orientation defined for each section embedded. In the case of alopecia assessment, the punch biopsy is transversely rather than vertically sectioned; this method yields sections with numerous follicles, allowing evaluation of follicular density, follicular unit morphology, and follicular growth dynamics, i.e., anagen-telogen ratio[17]. Once embedded, depending on the tissue size, one to several profiles (5µ thick tissue sections) are cut from the paraffin tissue blocks, placed on a glass slide, and routinely stained with hematoxylan and eosin. In certain circumstances, such as clinical impression or pathologic suspicion of scabies, Grover's disease, dermatitis herpetiformis, or folliculitis, level or serial sections (typically 3 glass slides with tissue sections from deeper levels of the biopsy) are performed to increase the yield of identifying diagnostic findings of focal pathologic processes. In addition, other histochemical stains can be applied to the tissue for identification of specific organisms or tissue components. Some commonly used histochemical stains include periodic acid Schiff with or without diastase (fungus, basement membrane), Grocott's methamine silver (fungus), Fite's acid fast bacillus (mycobacteria), alcian blue or colloid iron (mucin), Prussian blue (iron-hemosiderin), trichrome (collagen and smooth muscle), and Fontana Masson stain (melanin). **See figure 3**.

Reporting clinical information

Successful diagnosis of skin pathology requires, perhaps above all else, effective cooperation, and teamwork, between the clinician and the dermatopathologist. Not only providing a diagnostic tissue sample by the best possible procedure, but also by conveying relevant clinical information does this. **See figure 4**. Clinical information is invariably helpful and often absolutely essential to the histologic diagnosis of skin disease, especially inflammatory dermatoses. Many lesions may appear identical under the microscope and therefore require the background information for proper discrimination. **See figure 5**. In general, increased and effective communication between clinician and pathologist results in more accurate diagnosis and treatment for the patient, and this begins with the relatively brief yet informative specimen submission/requisition form. At the bare minimum, five pieces of information should accompany every dermatologic specimen for pathologic evaluation: "Description, Demogrpahics, Duration, Diameter, and Diagnosis"[15]. The description may include scarcely more than a word or two regarding the general appearance of the lesion as seen grossly on the patient (e.g., erythematous, scaly, pearly, raised, ulcerative etc…). Demographics must include at

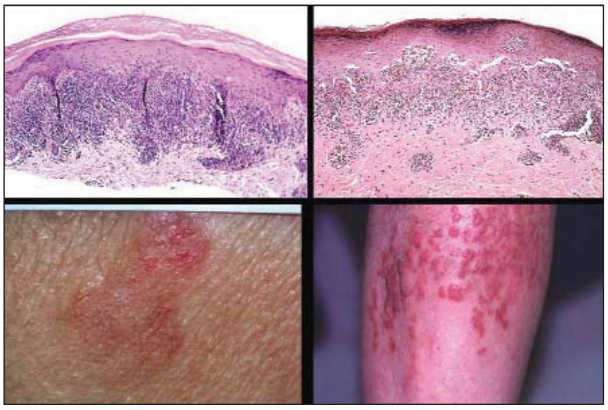

Fig 5. The skin reacts in a limited number of ways, distinguishable by light microscopy, so for any given pathologic change, several possible causes exist. By clinical correlation, the differential diagnosis may be limited to one or two entities. Illustrated here are two examples of lichenoid dermatitis: on the left is a biopsy from lichen planus-like keratosis (LPLK or benign lichenoid keratosis) and on the right is biopsy of from lichen planus. If the dermatopathologist is informed that the biopsy was done for suspected skin cancer, then this lichenod dermatitis would be interpreted as a "LPLK". In contrast, if the clinical information provided was generalized pruritic eruption of polygonal, erythematous, slightly violaceous papules, the diagnosis of lichen planus would be rendered.

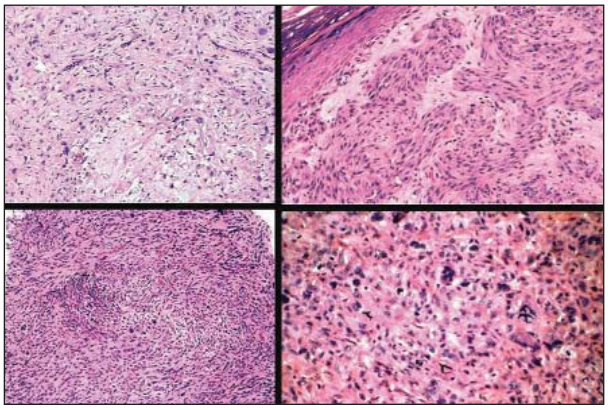

Fig 6. Cutaneous malignant spindle cell neoplasms. Depending the degree of differentiation and co-existence of precursor lesions (solar keratosis, melanoma in situ), it may be impossible to reliably distinguish atypical fibroxanthoma ((AFX) a.k.a. superficial malignant fibrous histiocytoma)(bottom panels) from spindle cell counterparts of melanoma (top right panel) and squamous cell carcinoma (top left panel). In situations such as this, immunohistochemistry is used to distinguish specific tumors froßm one another.

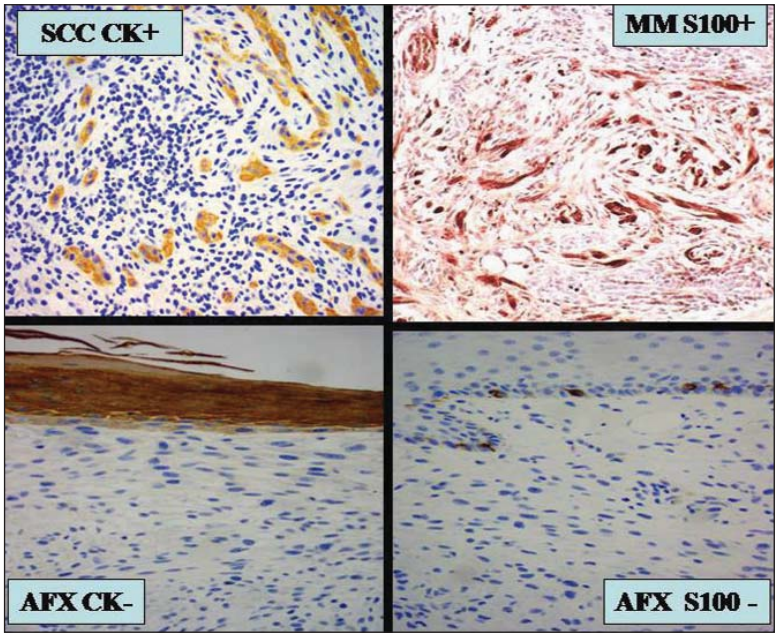

Fig 7. Immunohistochemistry for cutaneous malignant spindle cell tumors. Atypical fibroxanthoma ((AFX) (bottom panels) is distinguished from spindle cell variants of melanoma (top right panel) and squamous cell carcinoma (top left panel) by the absence of cytokeratin (CK) and S100 protein (sensitive melanoma marker) expression.

least the age and sex of the patient, however in certain circumstances the race, medications and known medical history can also prove invaluable. Duration is often crucial in distinguishing subacute from more chronic or acute processes. The diameter of the lesion is particularly helpful when the lesion has been only partially excised. For eruptions, one may substitute "distribution" over the body for diameter. Finally, the clinically suspected diagnosis and differential should be included for it is the dermatopathologist's ultimate goal to bring in line the histologic morphology with the clinical impression. Although some clinicians purposefully withhold this last "D" (diagnosis), in an effort to avoid biasing the pathologist, it is the burden of the pathologist to avoid this pitfall, and to maximize the utility of the clinical information. In order to avoid bias, dermatopathologists do not read the clinical information until after review of the histologic sections. In this fashion, the dermatopathologist generates a histologic differential diagnosis that can be reconciled with the submitted clinical differential diagnosis.

Special attention is warranted to a few specific vagaries commonly encountered on pathology requisition forms. As referred to above, many clinicians unfortunately fall into the pattern of either leaving the clinical impression lines blank, or else employing vague and essentially meaningless terms such as "lesion" or "skin anomaly." Whether such practice indicates a dearth of clinical acumen, laziness, or mere oversight remains debatable; however, it undeniably results in limited clinicopathologic correlation and the potential to render an erroneous diagnosis that could lead to therapeutic misadventure. Indicative of the significance of including informative clinical information, are the results of a recent study from the Cleveland Clinic[8, 21]. Dermatologists, whose residency training includes extensive exposure to dermatopathology, were more than 20x less likely to omit pertinent clinical information when submitting specimens for dermatopathologic evaluation, as compared to family practicioners. Another unfortunately common practice to be avoided is use of the term "rule out" on a requisition form. The ambiguity of the phrase is easily appreciated when one considers its typical meaning as indicative of the suspected lesion (i.e., "please rule out basal cell carcinoma because that is what I think it is") or the exact opposite (i.e., "I do not think it is basal cell carcinoma however please rule it out to be sure")[21]. Although seemingly obvious, in the fast paced and high-pressure practice of modern clinical medicine, the task of filling out the clinical suspicion is often relegated to clinical staff in place of the submitting physician (e.g. nurses, technical staff, etc. …). This practice should be avidly avoided due to the complexity and importance of such information to the dermatopathologist. Lastly, the use of obscure or even made-up abbreviations is also to be avoided due to the resulting obligatory phone calls and unnecessary communiqué, which slow down the diagnostic process[21]. In essence, biopsy is a physician-to-physician consultation; therefore the dermatologist should be communicating to the dermatopathologist the most relevant clinical information to assist in arriving at correct diagnosis.

On a final note, there is the question of submitting digital imaging of the gross lesion along with the specimen for histologic analysis. Rapid advancement in digital imaging has drastically reduced the time and cost associated with submission of photographs of the lesion on the patient. Furthermore, increasing resolution continues to improve, which only serves to raise future expectations for clinicopathologic correlation. A recent study from Hershey Medical Center[22] showed that inclusion of clinical photos helped confirm initial diagnoses and narrowed differential diagnoses with statistical significance, and of note, inclusion of digital images with specimens did not change diagnoses or decrease the number of additional studies. The diagnostic contribution for digital images had the most impact on the diagnosis of inflammatory dermatoses: these images were "good help" in 43% of biopsies and narrowed the differential in diagnosis in 31%. Therefore, although not absolutely necessary, the submission of digital images with dermatologic specimens is strongly encouraged, particularly as the cost of digital images decreases while their quality increases.

Accurate biopsy interpretation

The dermatopathologist's role in dermatologic care is to identify the microscopic skin abnormalities and translate this information into a meaningful, clinically useful pathology report. Before histologic assessment, the dermatopatholigist must ensure that specimen number on the paperwork matches that on the glass slide and that the microscopic sections are reflective of the gross description (e.g. bisected punch biopsy will have 2 punch silhouettes on the slide). In general, when one views histopathologic sections, one should: 1) Be able to imagine how the lesion looked clinically. 2) Apply reliable and reproducible criteria for diagnosis. 3) Use clear and concise language that is clinically relevant in the report. 4) Keep an open mind as criteria evolve and new concepts arise. 5) Learn from errors as mistakes are inevitable (mistakes and malpractice are not equivalent)[1, 6]. All of the above entails a familiarity with normal skin and its variants (e.g., age-related changes, anatomic variations, the effects of exposure to the elements), familiarity with artifacts produced by processing and specimen handling/transport to avoid false-positive and negative results, an understanding of the natural chronology of various dermatologic diseases, being cognizant of the limitations of one's own skill and seeking outside consultation when appropriate, and keeping up to date with the constantly evolving knowledge of disease, criteria for diagnosis, and the elucidation of new dermatologic entities.

An approach as described above for histologic interpretation will manifest itself in a predictable algorithmic method[1, 6]. Dermatopathologic "sign-out" should be performed in a quiet place, free from distraction. Prior to using the microscope, the slide should be observed with the naked

Table 2. Skin inflammatory patterns and tissue reaction patterns

9 Basic Patterns of Inflammation	*Examples*
1) Superficial Perivascular	Drug reactions, viral exanthema
2) Superficial & deep perivascular	Lght reactions, lupus erythematosus
3) Vasculitis	Urticarial vasculitis, polyarteritis nodosa
4) Nodular & diffuse dermatitis	Lepromatous leprosy, xanthoma
5) Intraepidermal pustular dermatitis	Pustular psoriasis, candidiasis
6) Subepidermal vesicular dermatitis	Dermatitis herpetiformis,
7) Folliculitis & perifolliculitis	Suppurative folliculitis, rosacea
8) Fibrosing dermatitis	Scar, dermatofibromas
9) Panniculitis	Erythema nodosum, nodular vasculitis
Major Tissue Reaction Patterns	
• Lichenoid/interface (basal cell damage)	Lichen planus, erythema multiforme
• Spongiotic (intercellular epidermal edema)	Allergic contact dermatitis, pityriasis rosea
• Psoriasiform (regular epidermal hyperplasia)	Psoriasis, pityriasis rubra pilaris
• Vesiculobullous (blisters within or beneath epidermis)	Pemphigus, bullous pemphigoid
• Vasculopathic (vessel damage or occlusion)	Warfarin necrosis, hypersensitivity vasculitis
• Granulomatous (granulomatous infiltrates)	Sarcoidosis, granuloma annulare
Minor Tissue Reaction Patterns	
• Epidermolytic hyperkeratosis (hyperkeratosis with granular & vacuolar degeneration)	Epidermal nevi, keratoderma
• Acantholytic dyskeratosis (suprabasilar clefts with acantholysis and necrotic keratinocytes)	Grover's disease, Darier's disease
• Cornoid lamellation (column of parakeratotic cells)	Porokeratosis, incidental finding
• Papillomatosis (undulations & digitations of the epidermis)	Verruca vulgaris, solar keratosis
• Acral angiofibromas (increase of dermal vessels with surrounding fibrosis)	Fbrous papules (adenoma sebaceum)
• Flame figures (dermal eosinophils & eosinophilic material adherent to collagen bundles)	Eosinophilic cellulitis
• Transepidermal elimination (release of material via the epidermis or hair follicles)	Perforating folliculitis

Adapted from Weedon[2] and Ackerman' et al[1]

eye, taking note of the number of pieces of tissue and correlating this with how the specimen was grossed, and what type of biopsy is being examined (e.g., punch vs. shave biopsy). Importantly, as stated above, knowledge of the clinical history should be avoided prior to histologic examination, in order to avoid a biased approach. When the slide is placed under the scope, low magnification should be employed first for pattern recognition. First confirm the method of biopsy. The primary question then becomes whether the process involves an inflammatory or neoplastic infiltrate? Higher power should be used only later to evaluate cytology. While at low power, the anatomic site should be determined when possible (e.g., abundant compact orthokeratosis and absence of follicles is characteristic of volar skin) because certain disease favor some locales over others and some locales may predictably alter the appearance of the pathology (e.g., stasis changes co-existing with lower leg dermatoses and skin tumors). Clues to the age of the patient (e.g., solar elastosis from chronic sun exposure) should also be sought in order to alter the differential as some diseases favor pediatric patients and others more geriatric populations. At this point the dermatopathologist should apply their own personal systematic approach to examining all skin sections on the slide such as from top to bottom (stratum corneum to the basal layer of the epidermis to the dermis ending at the subcutis then examine for the pathologic pattern). The order is not important, but individual consistency is

essential to determine whether the lesion is due to inflammation, malformation, deposition or neoplasm. The major distinction is most often between an inflammatory or neoplastic process, which can often overlap as in the case of lichenoid host response to tumor such as melanoma.

Interpretation of inflammatory skin biopsies requires the identification and integration of 2 different morphologic features- the pattern of inflammation and the tissue reaction pattern[1, 2]. Some dermatopathologists base their diagnostic approach on the inflammatory pattern while others categorize biopsies into one of the major tissue reactions. In practice, an experienced dermatopathologists uses both methods simultaneously. **See table 2**.

In the case of neoplastic skin disease, benign neoplasms are easy to recognize and have super-imposable features, allowing for accurate and precise diagnosis. However, each malignancy has one or many features that are unique to it. Thus, particularly in the case for melanomas, widespread agreement on criteria for reliable and reproducible diagnosis, or concordance amongst experts does not exist [23]. Nonetheless, there is a constellation of morphologic features that one can commonly find in malignancies that leads to their diagnosis and/or a high degree of suspicion for their presence. See **table 3**. One key point to remember is that there is no single feature that reliably and reproducibly detects cancer. The diagnosis of malignancy is the summation of morphologic, clinical and molecular evidence. Immunophenotypic analysis of skin tumors also plays an important role in the distinction between poorly differentiated malignancies and spindle cell tumors. See **table 4** for the results of common antibodies employed in the skin, and **figures 6** and **7** for an illustration of their use for diagnosis.

Communication and clinicopathological correlation

It is always advantageous to examine histopathologic sections from the outset without reference to any clinical information, including the clinician's diagnosis. In this fashion, a pathologist is forced to make an analysis based on the powers of observation alone without the being biased by clinical impressions. Usually, a skilled dermatopathologist can formulate a meaningful diagnosis without assistance from the clinician, but when this is not possible, reference to the clinical data can aid in the evaluation of the biopsy. This method allows for accurate observations to be made and rational conclusions to be formulated without prejudice. If a clinical diagnosis differs strikingly from a histologic diagnosis, a pathologist should request additional sections, determine whether the specimens have been mixed up, consult with the clinician, or rethink the matter over the following day. In short, all attempts should be made to reconcile the findings on the slide with those on the patient.

On the other hand, once the dermatologist receives the dermatopathology report, the task of correlating the clinical findings with pathologic findings begins. If the pathologic findings are supportive of the clinical findings, the dermatopathology consult was immediately rewarding. However, if the pathologic findings cannot be reconciled with clinical findings, then a dialogue with the dermatopathologist should begin and all efforts to reconcile the gross with the microscopic be made.

The future of skin biopsy

Elucidation of the human genome, the burgeoning field of proteomics, the new science of bioinformatics and development of highly sensitive and accurate, and high throughput technologies such as laser capture microdissection, mass spectroscopy, DNA and tissue microarrays are leading a revolution towards the molecular screening, diagnosis, and management of cancer[11, 24, 25]. Molecular diagnosis is the detection of pathogenic mutations in DNA or RNA, or the associated protein in order to aid in the detection, diagnosis, subclassification, prognosis, selection of therapy, and monitoring of response to that therapy[11, 24, 26]. These techniques have only become possible due to the abundance of knowledge that has been created over the last 50 years concerning the molecular events occurring in human cancers[27]. For instance, by outlining the signaling pathways that regulate cell growth, the cell-cycle, and apoptosis (programmed cell death), targets for anticancer drugs have been developed and have been shown to be effective for selected groups of affected patients. Three examples of targeted therapeutics include 1) trastuzumab (Herceptin, Genentech) for the treatment of HER-2/neu overexpressing breast cancer[28]; and 2) imatinib (Gleevec, Novartis Pharmaceuticals) for the treatment of chronic myelogenous leukemia featuring a bcr/abl translocation[29], gastrointestinal stromal tumors with selective c-kit oncogene–activating mutations[30], unresectable or metastatic dermatofibrosarcoma protruberans [31], and potentially a subset of melanomas [32]; and 3) epidermal growth factor receptor (EGFR) inhibitors such as cetuximab (Erbitux, ImClone), panitumumab (Vectibix, Amgen), and erlotinib (Tarceva; OSI Pharmaceuticals) for non-small cell lung cancers . (It's interesting to note that the EGFR inhibitor induced skin rash is significantly linked to overall and progression-free survival[33]). Introduction of these treatments into clinical practice has shown how the basic science of molecular pathogenesis of cancer can be translated into diagnostic, tissue based tests for the selection of patients for targeted therapy. For dermatology, the development of small molecule inhibitors targeting skin cancer-related protein kinases will likely make an impact on cancer management in the next decade[11, 34]. Protein kinases mediate most signal transduction pathways in malignant cells and result in increased proliferation, evasion of apoptosis, invasion, and metastasis and are one of the largest groups of drug targets accounting for 20% to 30% of the drug discovery programs at some biotechnology and pharmaceutical companies. Protein kinase inhibitors (e.g. imatinib) have the potential to be effective in the treatment of nonmelanoma skin

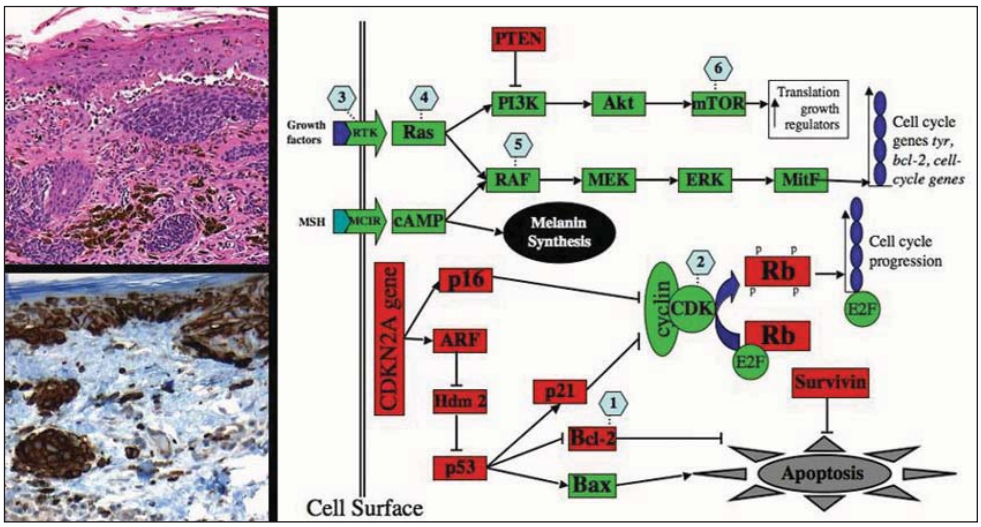

Fig 8. Pathologic assessment for aberrant expression of c-kit/CD117, a receptor tyrosine kinase RTK, labeled 3 in right panel), is frequently found mutated in melanoma arising in sun-damaged skin (lentigo maligna melanoma) [32]. Lentigo maligna melanoma arising on sun-damaged skin (top left panel) shows CD117/c-kit expression in both the in situ and invasive components, most melanomas lose c-kit expression with development of invasive/vertical growth phase, which has a potential to metastasize directionally related to its thickness (bottom left panel). Right panel shows an outline of the major molecular pathways in the pathogenesis of melanoma and potential targets (tagged by light blue hexagons) for small molecule inhibitors. Activating mutations of RAS are found in approximately 10-20% of melanomas; loss of PTEN in ~30-50%; activating mutations of BRAF in ~50%; Akt3 gene amplification and or activation in ~60% and ERK activation in a subset of melanomas. Arrows represent activation. Barred lines indicate inhibition. Numbered hexagons represent new small molecule inhibitors targeting cell-cycle specific steps that regulate melanoma cell growth: 1) antisense oligonucleotides to Bcl-2 (oblimerson); 2) CDK inhibitors (flavopiridol); 3) receptor tyrosine kinase inhibitors (Imatinib, gefinitib, erlotinib); 4) farnesyl transferase inhibitors; 5) RAF inhibitors (BAY 43-9006 (sorafenib); and 6) mTOR inhibitors (CCI-779). Akt: murine v-akt oncogene homologue. ARF: alternate reading frame. Bcl-2: B cell lymphoma derived protein. BRAF: v-raf murine sarcoma viral oncogene. cAMP: cyclic adenosine monophospate. CDK2NA" cyclin dependent kinase inhibitor-2A. CDK: cyclin dependent kinase. E2F: E2F cell cycle regulated transcription factor. ERK: extracellular signal-regulated kinase. Hdm2: human double minute-2. MC1R: melanocortin-receptor. MEK: (MAPK) mitogen activated protein kinase. MITF: microphthalmia transcription factor. MSH: melanocyte stimulating hormone (melanocortin). mTOR: mammalian target of rapamycin. PI3K: phosphatidynlinositol-3 kinase. PTEN: phosophatase and tensin homolog. RAS: rous avian sarcoma homologue. Rb: retinoblastoma protein

Table 3. Histologic features that differentiate benign versus malignant neoplasms

Benign	Malignant
Small	Large
Symmetric	Asymmetric
Well circumscribed	Poorly circumscribed
Smooth margins	Irregular, jagged margins
V-(wedge)-shaped; vertically oriented	No wedge-shaped profile
Superficially situated	Deeply situated
Non-ulcerated	Ulcerated
Neoplastic cells discretely arranged	Neoplastic cells in sheets
Aggregates small, uniform	Aggregates vary in size & shape
Cells well differentiated	Cells poorly differentiated
Adnexal structures usually preserved	Loss of adnexal structures
Maturation: nuclei of cells at base of lesion smaller than those at the surface	No maturation
No necrosis, or lonely, solitary cell necrosis	Necrosis en masse
No perineural invasion	Perineural invasion
No vascular invasion	Vascular invasion
No single filing of neoplastic cells	Single files of neoplastic cells between collagen bundles
Thick fibrous capsule at periphery	Poorly formed or absent capsule
Clefts between tumor stroma & normal stroma	Clefts between neoplastic cells and tumor stroma

Adapted from Ackerman[10]

Table 4. Immunohistochemical evaluation of poorly differentiated skin tumors

Antibody	Melanoma	Desmoplastic melanoma	Carcinoma	Sarcoma	Lymphoma
S100 protein	+	+	-	±	-
HMB-45	+	-	-	-	-
Mart-1	+	-	-	-	-
Cytokeratins	-	-	+	-	-
Vimentin	+	+	±	+	±
Leukocyte common antigen (LCA)	-	-	-	-	+
Actin	-	±	-	±	-
Epithelial membrane antigen (EMA)	-	±	+	±	-

cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, and systemic mastocytosis.

Personalized medicine includes the concepts that for a given disease, the rate of progression of the disease for each person is unique and each person responds in a unique way to drugs[24, 35]. With respect to melanoma as a dermatologic example, a personalized medical approach would include the detection of disease predisposition, screening and early disease diagnosis, assessment of prognosis, detection of minimal residual disease, pharmacogenomic measurements of drug efficacy and risk of toxic effects for treatment of metastatic disease, and the monitoring for melanoma recurrence[11]. Precise identification of melanoma patients at risk for death is the first step in developing efficacious melanoma therapies as the prognosis for individuals with metastatic melanoma is poor with a 5-year survival rate of 5-10%, due, in part, to the lack of effective treatment for metastatic melanoma which is chemoresistant. Melanoma is a good model for targeted therapy as its lesions (and precursors) are often available for sampling, which will be necessary to assess the presence or absence of therapeutic targets. **Figure 8** outlines the melanoma cell-cycle pathway and the proteins specifically targeted by these small molecule inhibitors.

Conclusion

Routine histologic examination of skin biopsy is a powerful, cost-effective (inexpensive) and widely available technique that is not readily replaced by other modalities for the diagnosis of skin disease. However, skin biopsy is not an analytic (black box) test like complete blood count (CBC) or serum cholesterol test that require little more than a blood sample and calibrated analyzer. Rather, procurement of a skin biopsy is a physician-to-physician consultation where the histopathologic findings are correlated with the clinical morphology and disease course to arrive at a relevant and accurate dermatologic diagnosis. This process cannot work without proper biopsy site and procedure selection, delicate and appropriate handling of the tissue, communication of pertinent clinical details, and discourse between the dermatologist and dermatopathologist. With the advent of new pathology based tests and delineation of the molecular and immunologic defects of dermatologic disorders, skin biopsy will likely play an increasingly greater role in the evaluation and management of individual patients.

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Review

Cutaneous Spirochetal Disease

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Introduction

Cutaneous Spirochetal Diseases - Unifying Features

- Portal of entry - skin or mucous membrane
- Systemic dissemination of spirochetes results in multiorgan involvement
- Multiple clinical disease stages interspersed with long latency periods (months to years)
- Histology varies with biopsy site and age of the lesion
- Causative organism - detected by special stains/ culture months to even years after primary innoculation

Although involvement of the skin in the more common spirochetal-induced diseases is clinically distinctive, making the correct diagnosis continues to remain an on-going challenge. Contributory factors include lack of systematic progression from one stage of the disease to the next, co-existence of manifestations of more than one stage in a patient at a given time and, initial presentation with symptoms of late stage disease. Other confounding variables include atypical clinical presentations and absence of serologic evidence of disease in patients with co-existing immunodeficiency disease such as human immunodeficiency disease (HIV)[1].

A. Borrelial Infection

These include Lyme disease and relapsing fever or febrile recurrens.

1. Lyme disease

Early manifestations - Erythema migrans

Initially called "erythema chronicum migrans Afzelius" because of its migratory nature, the name is now known to be a misnomer as the rash manifests within 3-30 days of the tick bite[2, 3, 4]. Erythema migrans (EM) may be seen anywhere on the body but is most common on the lower extremities, inguinal/axillary regions of adults **(Figure 1)** and, on the face in children ("slapped cheek" appearance)[5]. Women are reported to be more commonly affected in European studies[2]. Typically described as "round", the rash in reality is more oval with the "long line of the oval parallel to the lines of least skin tension" (Langer lines) **(Figure 2)**[6, 7, 8]. As migration of the rash proceeds, distortion of this configuration occurs **(Figure 3)**[9]. The center fades after a few weeks leaving only the annular border erythematous. The rash in itself is usually asymptomatic but 50% of patients complain of mild tingling, or itching[10]. Systemic manifestations reported in approximately 50% of patients, may appear[8] before, during or, after the classic rash[6, 9].

Multiple erythema migrans-like lesions occur in between 1-17% of patients[6]. The reported prevalence of multiple lesions is believed to be higher in the United States than in Europe[11]. Secondary EM lesions number from 2 to more than 80, usually occur away from the original lesion and, are usually smaller and non-migratory (occur in "crops" of similar size, color and shape) in comparison to classic EM[6]. Constitutional symptoms are usually more severe than those associated with classic erythema migrans[12]. A rare event, reminiscent of a Koebner-like phenomenon, is the development of chicken pox in an area previously the site of EM (**Figure 4**, personal communication S O'Connell, MD, UK).

Primary and secondary EM have an excellent prognosis attributable in part to the activation of pro-inflammatory cytokines such as interferon-γ[13]. The rash usually heals spontaneously but may persist for as long as 6-12 months (median duration of the rash in the United States is shorter than that in Europe)[2 14 10].

Histopathologic findings vary with the biopsy site[9] and age of the lesion. Biopsies of early lesions show papillary dermal edema and a mixed infiltrate of lymphocytes, neutrophils, few plasma cells and few eosinophils **(Figure 5)**. Biopsies of older lesions display a variably dense perivascular and interstitial infiltrate of lymphocytes and plasma cells **(Figure 6)**. Helpful, albeit non-specific, clues include the presence of plasma cells and mast cells in the infiltrate[15].

Fig 1. Erythema migrans in the groin with expanding margin at the site of the tick bite of a week's duration (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

Fig 2. Erythema migrans. Oval configuration of rash (courtesy of S Luger, MD, CT)

Fig 3. Erythema migrans. Distortion of oval configuration with migration of the rash (courtesy of S Luger, MD, CT)

Fig 4. Development of chicken pox in an area previously the site of erythema migrans ("Koebner-like" phenomenon, courtesy S O'Connell, MD, Southampton, UK)

Fig 5. Histopathology of early erythema migrans. Papillary dermal edema and a mixed inflammatory infiltrate. (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

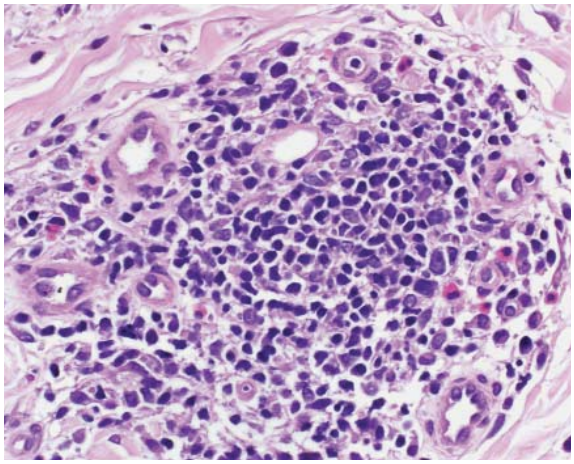

Fig 6. Histopathology of late erythema migrans. Dense perivascular lymphoid cell infiltrate with many plasma cell (hematoxylin and eosin stain, 40X) (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

The presence of both plasma cells and eosinophils in the same specimen is reported to be much less common than the presence of either[9]. From biopsy specimens, spirochetes are best located in the papillary dermis and may be short or elongate at this stage of the disease **(Figure 5 inset)**[9]. Direct detection of the spirochete from biopsy specimens by culture or by PCR typically has good sensitivity but is usually unnecessary[16].

EM - Histopathologic Highlights

- Histology - varies with biopsy site and age of lesion
- Early lesions - papillary dermal edema and a mixed inflammatory infiltrate
- Older lesions - variably dense perivascular and interstitial infiltrate of lymphocytes and plasma cells
- Clues - presence of both plasma cells and mast cells in the infiltrate
- Spirochetes - best located in the papillary dermis

Immunohistochemical studies indicate the infiltrate to be composed of CD4+ T lymphocytes with the exception of those seen in association with HIV infection in which the infiltrate is mainly CD8+ T lymphocytes (reflective of the CD4 lymphopenia of HIV infection)[17]. Histopathologic features of multiple lesions of EM are identical to primary EM.

Late Manifestations -
Acrodermatitis Chronica Atrophicans (ACA)

Observed mainly in elderly patients in Europe, ACA has an insidious onset and appears to have predilection for females[18]. An inflammatory phase presenting as a bluish-red discoloration on the extensor aspect of joints and lower extremity characterizes the early clinical stages of this biphasic disease **(Figure 7)**[19]. Lesions typically extend from distal to the proximal portion of the extremity involved. Although the erythema and swelling initially vary in intensity ('waxes and wanes'), swelling of the posterior aspect of the lower extremities is believed by some to be particularly indicative of Lyme disease **(Figure 8)**[10].

Cutaneous atrophy characterized by lesions with a "cigarette-paper-like" appearance **(Figure 9)** a feature of the later clinical stage is not an obligatory sequel to the inflammatory phase of ACA[19].

Central and peripheral nervous system involvement has also been documented in approximately 45% of patients with ACA[11]. Chronic joint and bone involvement is attributed to persistence of spirochetes in cutaneous lesions. The characteristic symptom, exhibited in about a third of the patients in one study, was a swollen or painful foot and heel[11]. Solitary or multiple fibrotic lesions near joints, particularly in the olecranon area, may develop in some patients **(Figure 10)**[19].

Histopathologic findings vary with the clinical phase of ACA. In inflammatory lesions, three layers are typically described: an atrophic epidermis, a zone of uninvolved papillary dermis and a layer of inflammatory cells composed of lymphocytes and plasma cells[20]. The presence of plasma cells in the infiltrate is documented mainly from studies from Europe as American reports indicate that few or no plasma cells are found[19, 21]. The infiltrate may be deep with extension into the subcutis[10]. Occasionally, interface dermatitis has been reported.

ACA - Histopathologic Highlights

- Two distinct clinical phases - early inflammatory phase and late atrophic phase
- Histopathology varies with clinical phase of the disease
- Inflammatory phase characterized by three layers
  Layer 1 - atrophic epidermis
  Layer 2 - zone of uninvolved papillary dermis
  Layer 3 - inflammatory infiltrate of lymphocytes and plasma cells
- Causative organism - detected by special stains/culture months to even years after primary innoculation

Unusual findings include the presence of vacuoles, either singly or in groups, at different levels of the dermis[22]. While some believe these represent mature adipocytes, others believe them to be an expression of lymphedema, given that they are mainly observed from biopsies of markedly edematous sites. In favor of the latter hypothesis is the absence of such vacuoles from the same site post-treatment.

All three species of *B. burgdorferi* that infect humans have been found in ACA lesions[23]. Phenotypic studies indicate the lymphocytes in the infiltrate are mainly of the CD4 phenotype, favoring the concept that ACA is a T-cell mediated immune response[24]. Further in support of this theory is the expression of adhesion molecules such as ICAM-1 on endothelial cells, lymphocytes and basal keratinocytes in the inflammatory infiltrate[25]. Chronicity of the lesions may be partially explained by downregulation of MHC class II molecules on Langerhans cells[26]. An ineffective anti-*B. burgdorferi* immune response essentially translates to ineffective elimination of the spirochete.

Cutaneous Scleroborrelioses

Sclerotic skin lesions clinically indistinguishable from primary lichen sclerosus et atrophicus (LSEA), morphea, progressive facial hemiatrophy/Parry-Romberg syndrome (PRS) or eosinophilic fasciitis/Schulman's disease ("borrelial fasciitis") develop in association with or in the absence of other dermatoborrelioses[27, 28, 12, 29, 30]. Periarticular ("ulnar") fibrous nodules, presenting as hard nodules on the lateral aspect of the digits near joints and described in association ACA, may also occur in the absence of it or any other dermatoborrelioses[31].

Fig 7. Acrodermatitis chronica atrophicans - early clinical stage. Bluish-red discoloration on the dorsum of the foot (courtesy of the late J White, MD, UK)

Fig 8. Acrodermatitis chronica atrophicans. Characteristic swelling on the posterior aspect of the lower extremities (courtesy S O'Connell, MD, Southampton, UK)

Fig 9. Acrodermatitis chronica atrophicans - late clinical stage. Typical end-stage cutaneous atrophy with prominence of superficial veins (courtesy S O'Connell, MD, Southampton, UK)

Fig 10. Acrodermatitis chronica atrophicans. Erythematous, fibrotic lesion in the olecranon area (courtesy S O'Connell, MD, Southampton, UK)

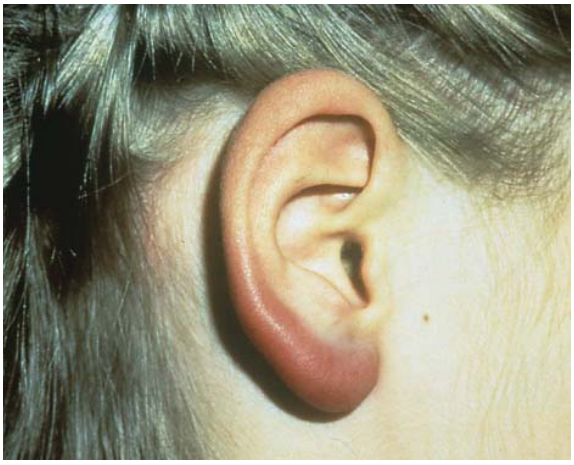

Fig 11. Borrelial lymphocytoma of ear lobe, three months duration (courtesy of the late J White, MD, UK)

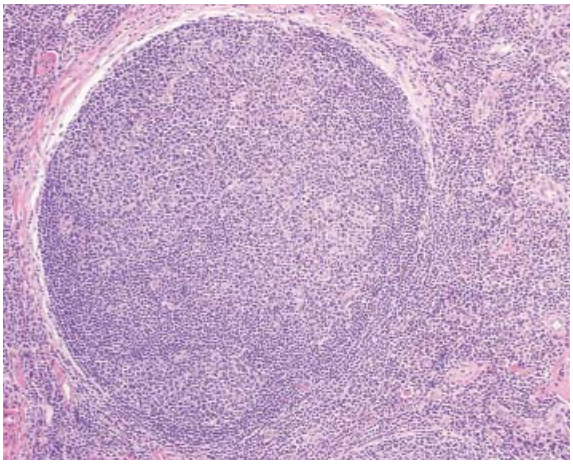

Fig 12. Cutaneous borrelial lymphocytoma with definitive history of tick bite. Nodular and dense lymphohistiocytic infiltrate with prominent germinal center (hematoxylin and eosin stain, 40X)

Lesions clinically resembling LSEA/scleroderma present with histologic features of the same. A unifying feature of LSEA- and morphea-like scleroborrelioses is the abundance of plasma cells in the inflammatory infiltrate[19]. Unusual histologic findings include a scleromyxedema-like picture with increased dermal mucin and fibroblast proliferation[31].

Histopathologic examination of a periarticular fibrous nodule reveals a relatively well-circumscribed nodules of broad hyalinized bundles of collagen with macrophages and plasma cells[32, 33]. Adjacent capillaries may be occluded by similar deposits.

Progressive facial hemiatrophy and eosinophilic fasciitis show variable dermal sclerosis, loss of appendages and a perivascular infiltrate composed predominantly of lymphocytes and plasma cells with scattered histiocytes[10]. Features specific to borrelial fasciitis are that eosinophilic infiltration of the fascial planes is not as impressive as in "idiopathic" Schulman's disease[29].

Cutaneous Atrophoborrelioses

Atrophic lesions indistinguishable from primary anetoderma may also occur in the absence of other dermatoborrelioses[34 19]. When associated with ACA, these lesions are usually seen at the periphery of an extensive lesion[35].

Biopsy specimens from atrophic/anetoderma-like skin lesions show absence of elastic tissue fibers in association with a perivascular infiltrate of lymphocytes with occasional histiocytes, neutrophils or eosinophils[19]. Spirochetes are found with difficulty in histologic sections.

Cutaneous lymphoborrelioses
(B- and T-cell lymphoid hyperplasias)

The least common of the cutaneous hallmarks of Lyme disease (1%), lymphocytic infiltrates associated with *borrelia* may present either as single (lymphadenosis benigna cutis solitaria, LABC solitaria, borrelial lymphocytoma) or, as multiple lesions (LABC dispersa)[10]. More common in children than in adults, LABC clinically presents as a nodulo-papular lesion in the ear lobes **(Figure 11)** in children and the nipple-areolar area in adults[12]. The precise reason for this predilection is not known but may be tissue temperature-related[10]. The incubation period varies anywhere from a few weeks to 10 months. The duration of an untreated solitary lesion can vary anywhere from months to years (average 5 years)[36]. Spontaneous resolution may occur in months or years but typically, lesions resolve more rapidly with antibiotic therapy[11]. Lesions of LABC-dispersa can be entirely subcutaneous, may last for decades, and typically have no specific site predilection or associations with other dermatoborrelioses. LABC has been reported solely in Europe. However, all three species of *B. burgdorferi sensu lato* have been associated with LABC so it is unclear whether the lack of U.S. cases is related to strain differences[23].

Several reports suggest an association of low-grade cutaneous B-cell lymphoma with *B. burgdorferi* infection[37, 38]. Clinical presentation of borrelia-associated B-cell lymphoproliferative disease is varied and consists of multiple ill-defined, slowly progressive, plaques and nodules presenting on the trunk and/or extremities of usually older patients.

Histologic features in both benign B- and T-cell dominant lesions are essentially similar to benign lymphoid hyperplasias **(Figure 12)** secondary to an arthropod bite, vaccination or other causes. Briefly, these include a dense, deep dermal, predominantly lymphocytic infiltrate with admixed plasma cells and eosinophils. The presence of scattered follicles with tingible body macrophages, mitoses and a polymorphous infiltrate ("reactive germinal centers") are helpful clues to the reactive nature of the infiltrate[10]. In cases where germinal centers are absent, immunohistochemical studies definitively prove the polyclonal nature of the infiltrate. In order of frequency of Borrelial infection marginal zone lymphoma (20-52%) is followed by follicular center lymphoma (15-26%) and diffuse large B-cell lymphoma (16-15%)[37, 39].

That antigenic drive by borrelia may be a pathogenic factor in more than one subtype, is supported by the association of *B. burgdorferi* with multiple subtypes of cutaneous B-cell lymphoma. Demonstration of the organism in the skin prior to development of overt cutaneous B-cell lymphoma serves to confirm the temporal progression of *B. burgdorferi* - associated B-cell lymphoproliferative disease. Clinical regression of marginal zone lymphoma after eradication of *B. burgdorferi* argues in favor of a benign process[40, 41, 38].

Definitive classification of borrelia-associated B-cell lymphoma is confounded by the immunohistochemical profile. Expression of CD5 and CD10 (CALLA), antigens typically associated with centrocytic lymphoma, are absent in borrelia-associated B-cell lymphoma[37].

Cutaneous lesions other than those reported above have been reported in patients with documented Lyme disease **(Table 1)**[8]. These include panniculitis, vasculitis, granuloma annulare, erythema multiforme and a syphilis-like papulo-squamous eruption. The association of these lesions with *B. burgdorferi* infection is at the level of case reports and *B. burgdorferi* has not been directly recovered from the infected areas of any of these lesions. As such, systemic *B. burgdorferi* infection may be a precipitant of pathways leading to the development of these lesions in rare instances.

Fig 13. Primary syphilis. Penile chancre (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

Fig 14. Secondary syphilis. Macular rash involving palms (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

Fig 15. Secondary syphilis. Macular rash involving soles (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

Fig 16. Secondary syphilis. Condyloma lata involving genitals (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

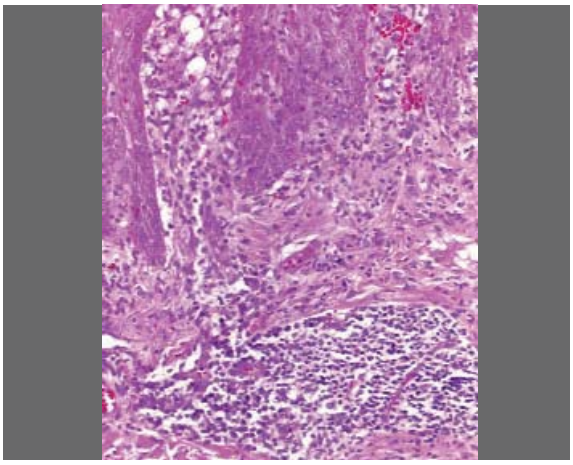

Fig 17. Secondary syphilis. Irregular epidermal hyperplasia (lichen planus-like) and dense underlying perivascular and interstitial lymphoid cell infiltrate (hematoxylin and eosin stain, 10X) (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

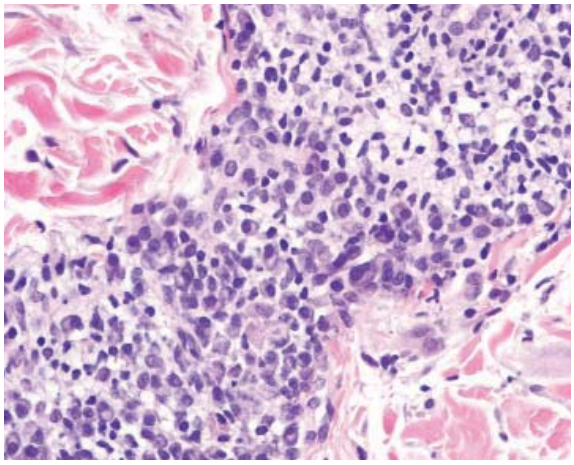

Fig 18. Secondary syphilis Plasma-cell rich inflammatory infiltrate (hematoxylin and eosin stain, 40X) (courtesy of R Rapini, MD, TX)

Uncommon Cutaneous Manifestations of Lyme Disease

- Cutaneous scleroborrelioses
  - Morphea
  - Lichen sclerosus et atrophicus
  - Periarticular fibrous nodules
  - Progressive facial hemiatrophy
  - Eosinophilic fasciitis
- Cutaneous atrophoborrelioses
  - Anetoderma
- Cutaneous lymphoborrelioses
  - B-cell dominant (including B-cell lymphoma)
  - T-cell dominant
- Others
  - Panniculitis
  - Granuloma annulare
  - Erythema multiforme
  - syphilis-like papulo-squamous eruption

2. Febrile Recurrens

Far less common than Lyme disease, febrile recurrens is also characterized by an initial erythema migrans-like bite reaction ("central nodule with a distinctive brownish ring") and initial viremia, typically does not have as long a clinical course[42]. Typically, there may be anywhere from 3 to 10 recurring febrile attacks which means a disease lasting from as few as 21 days to as many as 140 days (5 months) but essentially no longer. The variability in clinical course of febrile recurrens is believed to be due to antigenic phase variations undergone by relapsing fever borreliae[42].

B. Treponemal Infections

These include syphilis, pinta, yaws and endemic syphilis. Syphilis, the best known of these four, is a venereal disease and thus presents with initial manifestations in the genital area, while the other three, collectively known as the non-venereal treponematoses, are not spread by sexual activity and thus do not initially manifest in the genital area. Since essential morphologic and serologic differences are not fully recognized between the different treponematoses, clinical history including geographic differences is crucial to differentiating and recognition of each of these entities.

Primary Syphilis - Histopathologic Hightlights

- Erosion or ulceration
- Dense, predominantly perivascular, inflammatory infiltrate of lymphocytes and plasma cells
- Spirochetes - located in almost all cases

Syphils

While Lyme disease is the most recently recognized of the spirochetal diseases that affect humans, syphilis historically remains the better known. Parallels are often drawn between these two entities and justifiably so, given that both diseases are caused by spirochetes, start with a primary lesion, affect multiple organ systems including the skin and run a chronic course[43]. Also, while spontaneous healing of the primary lesion may occur in either, in both years without symptoms may be followed by new manifestations.

Perhaps a consequence of the reduced morbidity associated with HIV infection, recent epidemiological reports have shown a resurgence of syphilis both in the United States and Europe[44].

Early Manifestations (primary syphilis)

The chancre, the characteristic initial lesion of primary syphilis, occurs about three weeks after the initial inoculation, is highly infectious, and usually presents as a small painless ulcer on the genitals **(Figure 13)**[45]. The classic Hunterian chancre ulcer, fully developed in about two weeks and typically persisting for 2-6, is a sharply demarcated round or oval papule, measuring about 2 mm in diameter, with rolled edges and a clean eroded surface. In men it is predominantly located on the penis (glans, the coronal sulcus and prepuce) and women, the labia majora and minora, cervix, fourchette and perineum are involved in decreasing order of frequency. "Kissing chancres" may develop in areas of skin-to-skin contact. Extragenital chancres (on the lips and oral mucosa) are increasingly being reported[44]. The presence of a palpable, unilateral satellite lymph node is a helpful clue to the etiology of the lesion. Spirochetemia is believed to precede onset of development of the ulcer.

The primary lesion is histologically characterized by an erosion or ulceration with a fibrinopurulent exudate covering the surface 46. Hyperplasia of the adjacent epidermis with or without spongiosis may be seen. A predominantly perivascular, dense, inflammatory infiltrate of lymphocytes and plasma cells and reactive endothelial cell atypia are believed to be integral features. Rare cases with fibrinoid necrosis of vessel walls have been noted.

Fluorescent antibody staining using immunohistochemistry is believed to be more useful than special stains in detecting the causative organisms in early lesions[47, 48, 47]. In the absence of identification of the spirochete, serologic testing is essential. Reaginic tests may however be negative (20% of cases) or reactive at low titers in patients with primary syphilis.

Secondary Syphilis

The eruption of secondary syphilis typically develops 3-12 weeks after the primary chancre and is bilateral, symmetric, more prominent on the upper extremities and involves the palms **(Figure 14)** and soles **(Figure 15)**[49, 50]. The rash may be macular, papular or papulo-squamous pruritic or non-pruritic eruption, and usually involves

skin and mucous membranes[51]. Condyloma lata are moist papular lesions that coalesce to form plaques and are typically located on the genitals **(Figure 16)**, perianal area and axilla[52]. Nodular lesions are not entirely uncommon and continue to be reported despite the overall decreasing prevalence of secondary lesions[53]. Pustular secondary syphilitic exanthemata have also been known to occur and based on clinical morphology may be miliary, large acneiform, flat pustular, or pustoloulcerative [54, 55]. Alopecia syphilitica, referring to the moth-eaten, irregular pattern of patchy hair-loss sometimes seen in secondary syphilis, is rarely seen now-a-days[56].

Uncommon secondary cutaneous manifestations include condyloma lata involving the toe webs, "horny syphilid" (characterized by discrete, hyperkeratotic lesions on the volar aspect of palms and soles), papulo-nodular lesions clinically mimicking histioid leprosy, targetoid or erythema multiforme-like lesions, pseudo-lymphomatous, papulonodular lesions and follicular lesions[52, 57-61]. Vegetating syphilid, refers to a variant that appears during the late stages of secondary syphilis and includes extensive, annular plaque-like lesions that may be verrucous[44]. "Malignant syphilis", a rare, ulcerative variant of secondary syphilis also known as lues maligna, is believed to be a result of an impaired cell-mediated immune system, is clinically characterized by verrucous, ulcerative, infiltrative granulomatous pigmented lesions primarily involving the face[62-64]. In the largest series reported from a single center, five of the six patients with lues maligna were HIV positive[65].

The old adage that syphilis is a great mimic is perhaps as true for its histopathologic features as it is for its clinical presentation[66, 67, 67]. The variation in histology of lesions of secondary syphilis is believed to be dependant on clinical morphology and spatial relationship of the eruption to infection[68].

The histopathologic features of papular lesions, both early and late, are believed to the most diagnostic and that of macular lesions non-specific[69]. Overall epidermal change is minimal in macular lesions[51]. Epidermal change is varied and may be spongiotic, irregular (lichen planus-like, figure 17) or psoriasiform (with neutrophilic parakeratosis and epidermal pallor) with or without exocytosis[70, 51]. In one study, keratinocytes necrosis (63%) and exocytosis (84%), found in a large proportion of biopsies studied, were defined as "constant" histologic features[70].

Although dermal changes are varied, unifying, albeit not entirely specific, histologic features include endothelial cell-lined vascular proliferation, reactive atypia and the presence of a plasma cell-rich inflammatory infiltrate **(Figure 18)**. The composition and depth of the infiltrate can vary from area to area within a single biopsy. Erythema multiforme-like lesions are characterized by vacuolar interface dermatitis with necrotic keratinocytes[59]. While plasma cells are typically found in the peripheral portion of the infiltrate, their presence in the inflammatory infiltrate is not invariable. While one study documents their presence in 23/27 cases (85%), yet another found them to be minimal or absent in 15/64 cases (approximately 25%)[66, 70]. Numerous plasma cells have been noted in the perivascular infiltrate of nodular seronegative lesions of syphilis in patients with HIV infection[71, 72]. An unusual, but useful, finding is the presence of intra/peri-neurial plasma cells found in 12% of cases in one study[51].

Secondary Syphilis -
Histopathologic Hightlights

- Varied histologic patterns
  - Epidermal change
    - Lichen-planus like
    - Psoriasiform
    - Spongiform
  - Dermal change
    - Lichenoid
    - Diffuse dermatitis
    - Granulomatous
- Unifying features
    - Keratinocyte necrosis
    - Exocytosis
    - Endothelial cell–lined vascular proliferation
    - Reactive endothelial cell atypia
    - Plasma cell-rich, predominantly perivascular, infiltrate
- Spirochetes - best located within epidermis and in blood vessels of the superficial plexus

Other reported changes include the presence of a granulomatous infiltrate that may be epithelioid (with or without giant cells) **(Figures 19, 20)** and papillary dermal edema[51, 70]. Cases of secondary syphilis with histologic features essentially similar to benign lymphoid hyperplasias secondary to an arthropod bite, vaccination or other causes have been known to occur **(Figure 21)**[60, 73]. Uncommon findings include a perineural infiltrate **(Figure 22)** mimicking histioid leprosy[61], Sweet's like neutrophilic dermatosis[51], obliterative vasculitis of medium-sized vessels at the dermal-subcutaneous junction with prominent karyorrhexis, noted in lesions of malignant syphilis[62] and cases with histologic features that "fit" the criteria for the diagnosis of a malignant cutaneous neoplasm (cytologic atypia, mitoses and dense infiltrate)[73].

The presence of spirochetes is typically seen in the superficial dermis and around blood vessels and has been reported in both typical and atypical lesions with the use of special stains such as the Warthin-Starry and Steiner in upto 70% of cases of secondary syphilis[74-76]. Ultrastructural studies showing scant treponemes substantiate the difficulties encountered in visualizing the organism by special stains[77]. Immunohistochemistry is a diagnostically useful ancillary aid in cases in which

treponemes are not visible with special stains[78, 79]. In support of this is a recent study demonstrating the presence of the causative organism in 12/19 cases (63%)[80]. An interesting finding in the same study was that the organism was found in the dermis and not the dermo-epidermal junction, a finding contrary to accepted teaching. Ultrastructural studies indicate the presence of treponemes not only in endothelial cells but also in the perineurium and endoneurium of peripheral nerves[77].

Cutaneous lesions of secondary syphilis are believed to be the result of immune response accompanied by the presence of antigen presenting cells and the influx of T. pallidum sensitized T lymphocytes produced during the primary stage of infection[81]. More recently, in vitro evidence supports the in vivo hypothesis that dendritic cells activated by T. pallidum play a key role in the TH1 response in secondary syphilis[82]. Mechanisms for increased angiogenesis in lesions of secondary syphilis have been attributed to elaboration of angiogenic cytokines such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF)[83].

Uncommon Cutaneous Manifestation of Secondary Syphilis

- Condyloma lata involving web spaces of toe
- Horny syphilids
- Histioid leprosy - like lesion
- Targetoid (erythema-multiforme-like) lesions
- Papulo-nodular lesions
  - Sweet's-like
  - Pseudolymphoma-like
- Vegetating syphilids
- Malignant syphilids

Tertiary syphilis

A variety of names (transitional, intermediate or precocious tertiary syphilis) have been historically used for manifestations of late-stage infection with overlapping features of secondary and tertiary disease[71]. Given that the clinical presentation and histopathology of secondary and tertiary syphilis are quite similar, distinguishing the two stages is often impossible. Further compounding is the fact that late lesions may occur anywhere from three to 35 years after the original infection[84].

Although late lesions are overall rare, the most common (75%) manifestations of tertiary syphilis ("syphilid") are gummatous (gummatous syphilid) lesions of the skin[85, 86]. Mucosal lesions may also occur but are relatively uncommon. Clinically, gummas are painless, firm subcutaneous nodules that occur almost anywhere on the body. Secondary ulceration is not an uncommon phenomenon[85, 86]. Gummatous syphilis may become nodulo-ulcerative (nodulo-ulcerative syphilid) lesions[87, 88]. The latter begin as asymmetric reddish-brown nodules with a predilection for the face, trunk and extensor aspects of extremities and progress peripherally to form serpiginous (arciform or polycyclic lesions) lesions. Papulo-squamous lesions have also been noted in tertiary syphilis as have granuloma annulare-like lesions[85, 89]. Syphilids typically resolve to form non-contracting scars with hyperpigmentation[87]. Grouped violaceous papulo-nodular lesions have also been reported[71].

The histopathology of a gumma is that of a granulomatous dermatosis with foci of caseation necrosis, an associated inflammatory infiltrate of lymphocytes and plasma cells and thickened vessel walls with reactive endothelial cell atypia. While granulomas may also be seen in nodulo-ulcerative syphilid, these are typically smaller than those observed in gummas, lack caseation necrosis, a prominent feature of gummatous lesions and, may even appear "sarcoidal"[85]. Lesions that resemble granuloma annulare clinically, have histologic features of the same[89]. Cases in which plasma cells are not present have been reported[86]. Definitive diagnoses can only be made by identification of the spirochete in tissue sections, positive cultures or positive serology.

Like secondary lesions, late lesions are believed to be the consequence of an immune-complex mediated phenomenon[81].

Non-Venereal Treponematoses

In addition to having a non-sexual mode of transmission, unifying features of the non-venereal treponematoses include similarities in the histologic features of lesions at different clinical stages of the disease. Given this, the histologic features of these three entities are addressed together with salient differences highlighted.

1. Pinta

The causative agent of pinta, Treponema carateum is closely related to the causative agent of the other treponematoses[90]. Despite this, features unique to pinta include the fact that clinically it only has cutaneous manifestations, are the least contagious of all the treponematoses and affects individuals of all ages[91]. Pinta is found only in the Western hemisphere including Southern and central America and Mexico.

The first clinical manifestation is a primary papule or plaque which typically appears 2-3 weeks after inoculation. Secondary skin lesions or "pintids" appear after three to nine months anywhere on the body and enlarge by local extension. Repetitive crops occur and are the reason pinta can remain infectious for years - far longer than any of the other treponemal diseases[90]. Both the primary and the secondary lesions are remarkable for the pigmentary changes they undergo which often persist lifelong. In contrast, the atrophic tertiary lesions, occurring after 1 to 3 years, are usually depigmented.

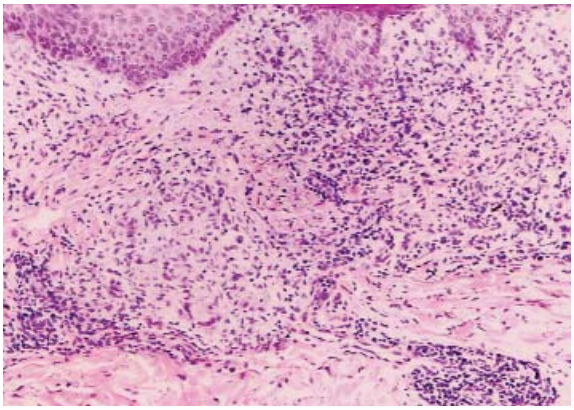

Fig 19. Secondary syphilis. Granulomatous lympho-histiocytic infiltrate with giant cells (hematoxylin and eosin stain, 40X) (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

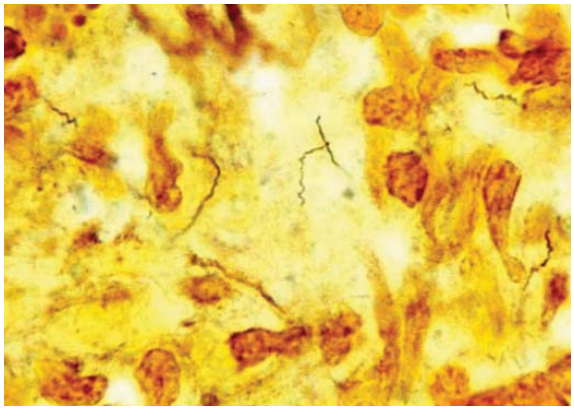

Fig 20. Spirochetes in the same biopsy stained with Warthin-Starry (oil immersion) (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

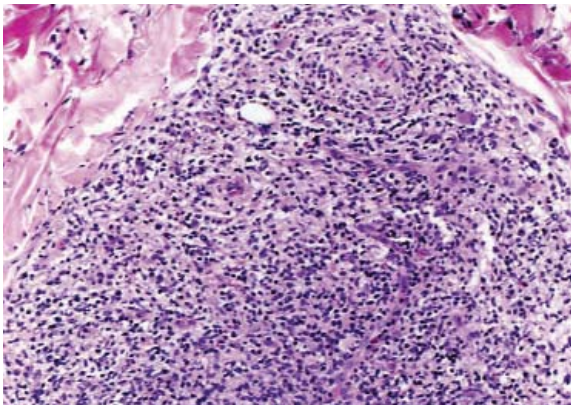

Fig 21. Secondary syphilis. Nodular lymphohistiocytic infiltrate (hematoxylin and eosin stain, 40X) (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

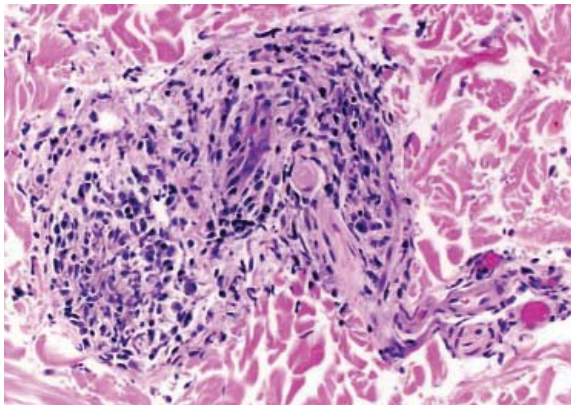

Fig 22. Secondary syphilis. Perineural lympho-histiocytic infiltrate mimicking leprosy (hematoxylin and eosin stain, 40X) (reprinted with permission from Dermatopathology Interactive Atlas, edited by Bhawan J, Sau P, Byers HR, 2001)

2. Yaws

Yaws, caused by Treponema pallidum subspecies pertenue primarily affects children, spreads by skin-skin contact and, occurs primarily in the tropics although rare cases from the United Kingdom have also been reported[90-92]. The initial lesion, teeming with treponemes, is a non-tender papule called the "mother yaw" that is often pruritic. It typically occurs in the lower extremity, develops about three weeks after the primary inoculation and persists for about three months. Clinically similar secondary lesions may follow and often involve the palms and soles (crab yaws)[92]. Late or tertiary lesions, developing in only a small proportion of patients (<10%), are nodular or ulcerated with occasional involvement of the underlying bone ("periosteitis").

3. Endemic Syphilis

The causative organism is Treponema pallidum subspecies endemicum. Like yaws, endemic syphilis more commonly occurs in children but, unlike yaws, is prevalent in dry, arid climactic conditions[90].

Clinically, endemic syphilis can be divided into an early and a late stage. The early stage comprises both the initial and secondary lesions as initial apthous ulcer-like mucosal lesions are usually not clinically discernable[93]. Disseminated "secondary" lesions involving the intertriginous areas are thus often the "first" manifestation of the disease. Tertiary disease is rare and typically does not involve the skin.

Histopathologic Features of the Non-Venereal Treponematoses

Early histopathologic changes of all of the non-venereal treponematoses are characterized predominantly by epidermal change in the form of mild acanthosis. Interface change with pigment incontinence is characteristic of the hyperpigmented lesions of pinta[91]. While endothelial cell atypia may be seen in pinta and endemic syphilis, it is not usually apparent in yaws. Intra-epidermal neutrophilic microabscesses, on the other hand, are a feature unique to yaws[46]. Late changes in all of the non-venereal treponematoses may be either acanthotic or atrophic[90]. Ultrastructural studies on achromic lesions of late pinta indicate hyperplasia of Langerhans cells[94]. In both early and late lesions treponemes may be visualized in the epidermis with the use of special or immunofluorescent stains, although achromic late lesions of pinta typically do not contain treponemes[46]. Given the overall lack of specificity of the histology of early and late lesions, definitive diagnoses of the non-venereal treponematoses can only be made by identification of the spirochete in tissue sections, positive cultures or positive serology.

Non-Venereal Treponematoses - Histopathologic Highlights

- Histology - varies with biopsy site and age of lesion
- Early lesions - epidermal change (mild acanthosis), papillary dermal edema and a mixed inflammatory infiltrate
- Older lesions - acanthotic or atrophic
- Helpful clues
  - Endothelial cell atypia - Pinta and endemic syphilis
  - Intra-epidermal neutrophilic microabscesses - Yaws
- Spirochetes - best visualized in the epidermis

Table 1. Cutaneous Manifestations of Lyme Disease

	ONSET	D/DX
COMMON MANIFESTATIONS		
Erythema multiforme	weeks-months (early)	arthropod bite, erythema multiforme granuloma annulare, urticaria, brown recluse spider bite
Acrodermatitis chronica atrophicans	months-years (late)	venous insufficiency, lichen sclerosus, scleroderma, physiologic age-related changes
UNCOMMON MANIFESTATIONS		
Cutaneous scleroborrelioses	months-years (late)	primary morphea, primary LSEA, rheumatoid nodule, gouty tophi
• **Morphea**		
• **Lichen sclerosus et atrophicus**	months-years (late)	primary progressive facial hemiatrophy/Parry-Romberg syndrome (PRS), primary eosinophilic fasciitis/Schulman's disease
• **Periarticular fibrous nodules**		
• **Progressive facial hemiatrophy**	months-years (late)	
• **Eosinophilic fasciitis**		
• **Cutaneous atrophoborrelioses**	weeks-months-years (early or late)	
• **Anetoderma**		primary anetoderma
Cutaneous lymphoborrelioses		arthropod bite reaction, response to vaccination, granulomas, neoplasm pityriasis lichenoides, polymorphous light eruption
• **B-cell dominant (including B-cell lymphoma)**		
• **T-cell dominant**		
Others		erythema nodosum, insect bite reaction drug eruption primary syphilis
• **Panniculitis**		
• **Granuloma annulare**		
• **Erythema multiforme**		
• **Syphilis-like papulo-squamous eruption**		

Conclusion

Given their common mode of entry and clinical course, it appears as if the pathogenic organisms of cutaneous spirochetal-induced disease share relatively unique virulent characteristics, a feature particularly striking in view of the diverse epidemiology of the different diseases detailed above. We appear to have made considerable progress in identification of the causative organisms and clinical features of most spirochetal diseases that involve the skin. While serologic testing is the diagnostic gold standard, the use of adjunct ancillary aids such as immunohistochemistry is strengthening the role of histopathology in discrimination of the various cutaneous spirochetal-induced diseases.

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