CHAPTER 1
The three acnes and their impact

The visibility of the lesions of acne vulgaris and acne rosacea as we present ourselves to the world and interact with others is a source of anguish to many. The hidden lesions of acne inversa (hidradenitis suppurativa) may interfere even with the most basic social interactions. The most profound effect of the acnes is on the psyche, so that aspect will be discussed "up front," but first we need to know what we are talking about.

1.1 Acne vulgaris

Vulgaris is a Latin word, an adjective that means *common*. It is not a pleasant term, but it is descriptive (even a little vulgar). It is also highly accurate because the lifetime risk of acne in developed countries with "Western" diets is 85–90% of the population. Indeed, acne vulgaris is so common that even senior dermatologists (who should know better) have stated, "Children as young as 7 years of age can present with mild, usually comedonal disease, which most often is a normal physiologic occurrence." To avoid embarrassing the author, no reference is provided.

If I agreed with the statement that acne is "normal" (or "physiologic"), there would be no point to this book. My purpose in writing it is to draw together numerous threads of information, from very old to very new. I want to define the problem. Then I want to explain how this disorder (and its relatives) arises. Only then can we sort out how to treat it (and its various types) in as logical a fashion as possible.

So let's get started—at the beginning.

Acne occurs when a plug forms in the follicular portion of the little oil gland and hair follicle organs on the skin called, in the older literature, *pilosebaceous units*. Here they will be called *folliculopilosebaceous units* (FPSUs), for reasons discussed in the Introduction.

There are other small organs that develop from the underside of the skin:

The eccrine sweat glands over most of our skin surfaces produce ordinary sweat.

The apocrine sweat glands in our armpits and groin areas produce a different kind of sweat, plus a peculiar class of chemicals called pheromones.

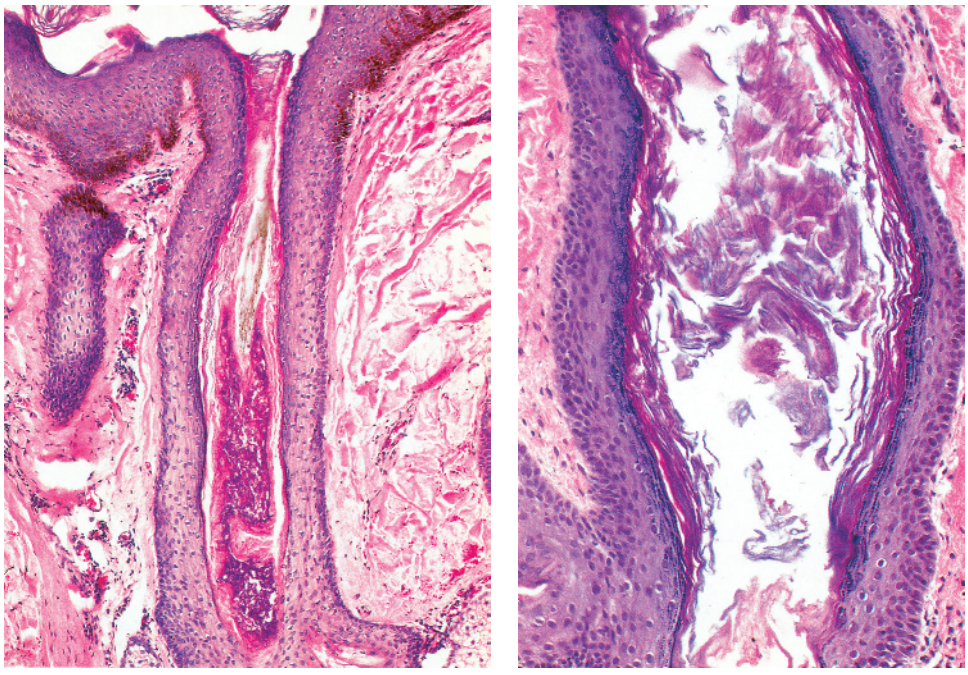
The mammary glands that form the breasts are derived in the same way, but obviously grow bigger than the others.

These are all referred to as *skin appendages*. They all have their own diseases, and some may be related to acne.

1.1.1 Terminology

The first plugs that lead to acne occur in the structurally quiet, non-inflamed, and non-infected follicular portion of the FPSU. The story starts with a stimulus to the development of a structure named the Follikel-Filament [1], the first tiny accumulation of the lining cells, the keratinocytes, in the follicular duct (Figure 1.1A). These cells produce the tough linear protein called *keratin* that makes up the surface of our skin. When formed into a long thin fiber, keratin makes hair, and when produced in thick flat compact sheets, keratin becomes nail. Thin sheets of keratin, made of individual terminal keratinocytes, form the surface of skin and line the follicular portion of the FPSU. The process of formation of keratin

Acne: Causes and Practical Management, First Edition. F. William Danby.



(A) (B)

Figure 1.1 (A) The first tiny accumulation of the lining cells, the keratinocytes, in the follicular duct. (B) Accumulation of these flat cells in the follicle leads to the microcomedo.

by keratinocytes in the follicular canal and on the skin surface is called *keratinization*. Normally, as these cells mature they separate from each other toward the center of the follicular duct, and the loose cells are released into the ductal canal where they are pushed to the top of the duct by the flow of sebum. Accumulation of these flat cells in the follicle leads to the microcomedo (Figure 1.1B). This growth progresses next with larger and larger masses of these lining keratinocytes, leading to the physical plugging of the duct. Next come microbial colonization and overgrowth of preexisting bacterial and yeast colonies. This continues at the same time as the increased plugging. The increase in intrafollicular mass causes expansion, leaking, and then rupture of the follicular unit.

The pilar unit is unaffected in early acne. It just keeps doing its job, which is to make hair, some of which may become trapped in the plugged and dilated follicular unit. That hair normally becomes increasingly coarse during the teen years, especially in boys, and has the effect of keeping the larger FPSUs open and uninvolved in the acne process.

The sebaceous unit is also growing and producing more sebum. At body temperature, that sebum is a liquid. It quietly percolates to the surface, through and around the plugs, and is responsible for von Jacobi–Pringle's "peculiar seborrhoeic condition," the oily skin of acne that we all recognize [2]. It also happens to be the preferred food for the organisms that come to live in the follicular unit, so that encourages their growth. Much more on them later (Section 6.0).

The leaking and rupture of the follicular unit of the FPSU are intimately involved with inflammation. This is a huge and very complex area. Hundreds of papers have been written on the subject. As of this writing, there have been 619 papers since 1952. I don't plan to review them all here, but you need to know that there is serious debate as to what starts the process. Does the plugging of the follicular unit come first, with pressure-induced leakage leading to inflammation [2]? Or does very early inflammation actually stimulate the plugging of the duct to produce excessive numbers of ductal cells [3]? My personal belief is that hormones plug the pore, and that causes the expansion that leads to the leaking,

which leads to the inflammation. My reasoning is simple: the organisms said to trigger the inflammation that triggers the keratinization are present in almost everyone, throughout life, and are in no greater number in acne patients than in normal persons [2]. If these organisms were the cause, we would all have acne, all the time. There has to be a factor that comes on at puberty, and generally leaves at the onset of maturity, in order to explain the timeline of acne in our population. More on that later (Section 2.6). There also needs to be a trigger that links the overproduction of the keratinocytes in the follicular duct to the onset of inflammation. That may be a recently described simple product of the pressure and hypoxia that build up in the follicular duct. More on that as well later.

Whether inflammation starts the plugging process or is a response to early leakage of materials from the FPSU, inflammation is seen as a target for therapy. For hundreds of years, physicians have been treating acne by trying to suppress the inflammation. I will try to convince you in this book that treating the inflammation is like chasing the horse after he has left the burning barn. Far more important is preventing the fire in the first place.

The "inflammatory process" doesn't just cause inflammation. It is often forgotten that its main chore is to *repair* the damage caused. Sometimes, the inflammatory process stops with simple healing of the wall of the follicular unit. In the *absence* of repair, the inflammatory reaction just keeps burning. Unfortunately, that leads to much more destruction. The contents of the dilated follicles leak or explode into the tissue under the skin surface. That causes more inflammation and leads to scarring. This prolonged destructive inflammatory activity is the cause of the tender nodules that are so ugly. Untreated, resolution occurs over a long time period, often years. This is referred to as "burning out" of acne. It leads to loss of parts of the FPSU, or the entire FPSU can be destroyed. It also leaves serious scarring behind.

1.1.2 The starting point

The primary target of acne therapy must be the prevention of the environment that produces the Follikel-Filament and so the microcomedo [1]. All the other events are "downstream" and secondary. These downstream events are called *epiphenomena*—things that happen "on top of" (that is what *epi* means) other things. Management of acne has for over a century concentrated upon suppressing these epiphenomena, while ignoring the real cause of the disease.

It is time to address the cause.

1.2 Acne rosacea

Classic acne rosacea is a variant of the acnes that shows up on the curved surfaces of the face (Figure 1.2). It is made up of blemishes centered on the openings of the follicular units of individual FPSUs. There are little raised bumps (folliculopapules) and very small pustules (folliculopustules). These little bumps and pustules are the "acne," and they appear on a rosy-red background, the "rosacea." The word *rosacea* has been used for a couple of hundred years as an adjective to modify the noun *acne*. So acne rosacea is really just rose-colored acne.

The word *rosacea* is now seen in the public eye and in some dermatological writing. The adjective has become a noun, and rosacea has become a "disease" or "condition" all by itself. See Appendix A for more on the name's change.

It is important to understand that acne rosacea actually has three separate components on the face. The first is the pimply acne, the second is the background redness (Figure 1.3), and the third is a thickening of the skin. There are also eye changes that cause a fourth, separate, but associated condition, but it is not always present.

Just as acne vulgaris always starts with plugs in the follicles that show up as comedones (blackheads) when mature, true acne rosacea always has the folliculopapulopustular lesions instead. Indeed, the presence of

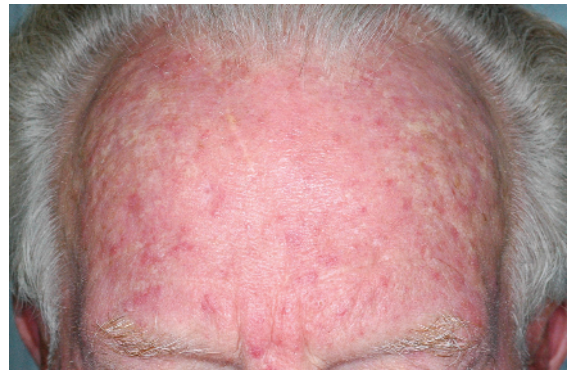


Figure 1.2 Acne rosacea loves convex, sun-exposed skin with a healthy population of well-stimulated FPSUs.

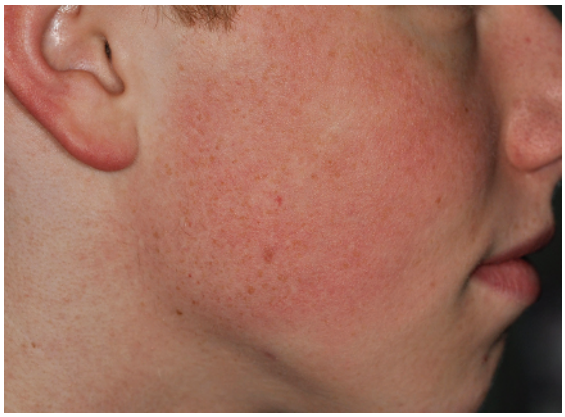


Figure 1.3 Some dermatologists consider this "pre-rosacea." Close inspection reveals a few comedones—almost normal in a 15 year old. He needs lifelong, truly broad-spectrum sun protection to prevent worsening of his actinic telangiectasia; a dairy-free diet; and a gentle topical retinoid.

visible comedones rules out acne rosacea as the prime diagnosis. Just to confuse the issue, there are occasional patients who have *both* acne rosacea and acne vulgaris.

1.2.1 The "pimply" part

The little bumps and pustules are caused by the body's immune systems (both of them) reacting to "stuff" that is caught in the pore. This is an automatic rejection reaction aimed at things like bacteria and yeasts, some tiny beasties called Demodex (see Section 6.4), and little ingrown hairs.

This reaction is the job of the innate immune system. *Innate* means *inborn* or *born with*, and it is the part of the immune system that does not need to "learn" what to do with foreign material. We are able, from birth, to recognize various foreign materials, and this part of the immune system is aimed automatically at anything in the pores or escaping under the skin from the pores that it recognizes as foreign material. It can be triggered by anything from tiny viruses to large ingrown hairs. (See Section 7.1.)

There is also a second part of the reaction caused by the "adaptive" immune system. Its job is to recognize, target, and eliminate foreign material when the innate immune system needs some extra help. It sometimes gets involved as well, but it takes a little while to get going, because it needs time to learn how to "adapt" to a new threat. There is much more on that to come (see Section 7.2).

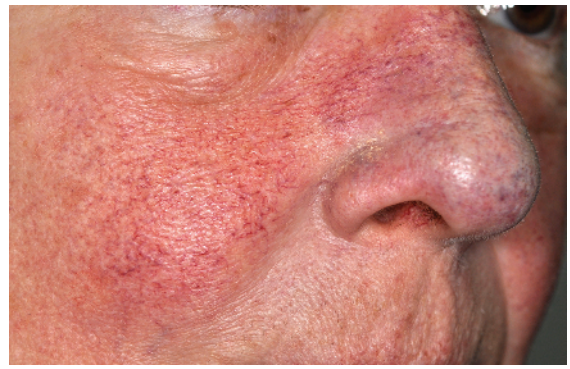


Figure 1.4 Longstanding sun exposure gradually weakens the collagen and other support tissues that wrap around and support the blood vessels, allowing them to dilate. The blood pools in them and turns dark, as on this man's nose.

1.2.2 The "redness" part

The redness (erythema) that causes the rosy color is made up of three separate components:

1. structural erythema,
2. functional erythema, and
3. inflammatory erythema.

The first, structural erythema, is due to dilated blood vessels. These are sometimes called *broken blood vessels*, but they are not really broken. Their structure is actually *dilated*, which just means they are increased in diameter and so are carrying more blood than usual as a result (Figure 1.4). More blood in the blood vessels makes the skin redder than usual. Structural dilation of a blood vessel is due to a gradual weakening of its walls that allows the blood vessel to bulge. Early bulging of very fine facial blood vessels is due to minor injury, most commonly from sun exposure. Even babies (who are usually protected against direct sunlight) will show pink cheeks. This is the earliest sign of *actinic telangiectasia*, the permanent and visible dilated blood vessels just under the skin surface. In a letter to the *British Medical Journal* in 1976, Dr. Ronald Marks stated that

> we have pointed out that the upper dermis in rosacea is quite abnormal and shows evidence of both solar elastotic degeneration considerably in advance of what might reasonably be expected for a group of middle-aged Britishers and other dystrophic changes that are not easily categorized. Autoradiographs after injection of tritiated thymidine and enzyme histochemical tests have suggested that small dermal blood vessels are also involved in rosacea (probably secondarily). It is my belief, based on these findings, that the primary disorder is a

> dermal dystrophy resulting from "weathering" (sun, wind, and cold) and an inherent susceptibility to this process. The dermal attenuation produced in this way causes lack of dermal support for the sub papillary venous plexus, allowing these channels (and the neighboring lymphatics) to dilate enormously. The flushing seen in rosacea is in all probability the result of the vessel dilatation - not its cause. The dilated vessels could become incompetent in addition as a result of the persistent and extreme pooling seen in them and this in turn may lead to diffusion of injurious macromolecules and mediators of the inflammatory process into the dermis. [4]

Dr. Marks labels this as a hypothetical process, with which I agree, but I can conceive of no other reasonable hypothesis that so neatly explains the features we see. Kligman supports this view in his essay on the subject, stating, "I, and others, regard rosacea as fundamentally a vascular disorder" [5].

In researching the literature while writing this chapter, I was delighted to find such valuable support for my working theory of the disorder (which follows shortly), but having read the supportive opinions of the experts, the next question of course must be "What is the vascular abnormality, and what causes it?" The question is neither addressed nor answered by Marks or Kligman. Instead, Kligman pointed out that the "histopathology of rosacea always shows the classic signs of damage to the dermal matrix, namely elastosis, collagenolysis, and increased glycosaminoglycans." He felt the changes were so similar to those seen in the advanced photodamage seen in the fair and often freckled skin of men of Celtic heritage that separating the two "is difficult and may be fruitless because the two may come together," but neither he nor Professor Marks went so far as to suggest that this actinic damage might extend to weakening of the other collagenous supporting tissues in the area. I strongly suspect that damage to the supporting material of the follicular portion of the FPSU occurs simultaneously as a concurrent or parallel process. Furthermore, I would be willing to suggest that both Kligman and Marks would be likely, upon reflection, to admit that as a possibility.

Indeed, the reason that rosacea and actinic damage "may come together," as Kligman wrote, is very simple. *I believe they are one and the same process*. The impact on dermal collagen causes wrinkles; the impact of sun on the collagen that wraps blood vessels causes the *blood vessels* to dilate, producing the condition called *actinic telangiectasia* (discussed in this section); and the impact on the collagen wrapping the FPSU allows the *follicular part of the FPSU* to dilate when subjected to internal pressure. And when a weakened follicle dilates, it bursts. Where does it burst? Exactly where you would expect—where the damage from the sun is at its worst—at the top of the follicle where the sun has its greatest impact. Older sun-exposed and collagen-damaged follicular units simply have no chance of making comedones, especially if they are the small short follicles in the superficial dermis of a fair-skinned Celt who doesn't have the deep and voluminous FPSUs that harbor deep aggressive acne. The follicular units of these shorter and smaller FPSUs simply leak or rupture first, producing the papules and pustules of classic acne rosacea because they cannot maintain their structural integrity long enough to progress to or support comedo formation.

Actinic means *caused by the sun's rays*, and *telangiectasia* is the condition of having lots of actinic telangiectases (the plural of *telangiectasis*, the word that describes the involvement of a single vessel). If you look closely, even with a magnifying glass, you will see only a pink blush in the early stages. As time passes, however, the little dilated vessels' walls absorb more ultraviolet light from the sun. That causes more sun damage. Extensive telangiectatic sun damage is easily observed on the cheeks of Peruvian children in the mountains near Cuzco, Peru. The combination of high altitude (about 3800 m) and daily exposure worsens and accentuates the damage.

To understand the mechanics of the problem, first take a look at a common garden hose to gain some insight into how blood vessels are constructed. There is an inner lining that forms a very fragile tube to carry the blood. Around that is a layer of supporting tissue that looks like the concentric woven strings you can see in the wall of a garden hose, and then there is the outside support material. Much of this support material in blood vessels is collagen. When collagen is damaged by ultraviolet light, it deteriorates. That is what causes wrinkles. Take a look at stained skin sections under the microscope, noting the pink and highly structured collagen in the dermis of young healthy skin, and then look at the gray-blue mush in sun-damaged skin. The same thing happens, I propose, to the fine supporting strings wrapped around blood vessels. With such loss of the original firm healthy structure, the blood vessels weaken further. That allows them to dilate, and so more blood will be carried. The vessels actually structurally expand

in cross-sectional area so they become big enough to be visible just by looking at them up close.

Over the years, these blood vessels can dilate hugely. They become visible at social distances or even from across a room. The tendency to develop this background facial redness is partly genetic, a point not lost on Prof. Marks and emphasized by Prof. Kligman, who estimated "that the prevalence may approach 35% in adult women of Scotch [*sic*]-Irish-Welsh Celtic ancestry." Further, he states, "I regard rosacea as belonging to the general class of photosensitivity disorders." Certainly, it is generally developed and worsened by sun exposure, so the fair and freckled part of the population is at greatest risk.

This vascular damage is not, by itself, acne rosacea. This is, purely and simply, actinic (or solar, if you prefer) telangiectasia—caused by photodamage that led to dilated blood vessels. It has no hope of clearing with oral antibiotics or topical creams, lotions, gels, foams, or ointments. The best treatment for structural erythema is preemptive and consists of

1 lifelong aggressive preventive sun avoidance,
2 use of true sunblocks such as hats and clothing, and
3 broad-spectrum (UVA and UVB) sunscreen to aggressively minimize the effects of unavoidable exposure.

Second best is active selective photothermolysis with laser or intense pulsed light (IPL) therapy. More on those later (Section 8.8).

The second component of the redness is *functional erythema*, and that relates to the increase in blood flow through the dilated blood vessels. The increased flow reflects temporary wider opening of the vessels. This comes and goes, and these temporary changes are of course reversible. The simple maiden's blush (and the even more embarrassing male counterpart) is a classic temporary high-blood-flow condition. It can come in seconds and vanish in less than a minute. The menopausal "flush" or "hot flash" that can be so embarrassing as a marker of "the change" is a more prominent and longer lasting (but still temporary) episode of high blood flow. Other longer lasting but temporarily dilators of blood vessels that cause functional erythema are sun, cold, wind, hot drinks and soups, caffeinated drinks, some drugs like niacin, and alcohol of all sorts.

And then there is a special third category of redness—that caused by inflammation. This is best called *inflammatory vasodilation*, and is both functional and structural. It is the *only* part of the redness that can actually be treated (even if only partly) with the medications generally used for "rosacea." If it is possible to get rid of the inflammation, the redness will fade to a certain extent. That will help reduce the color. That is where the tetracycline family of anti-inflammatory antibiotics can be very useful.

Note that decreasing or eliminating bacteria or yeast or Demodex-induced inflammation will reduce the associated inflammatory vasodilation but will not touch the redness from structural dilation. Note that the inflammation that causes the functional redness can also damage the walls of the blood vessels, further weakening them and contributing even more to the structural dilation of the blood vessels.

So why is this important? It is absolutely essential that patients understand that only *part* of the redness will respond to medications. I have seen dozens of patients over the years who have been on long-term antibiotics and numerous other medications, either topically or by mouth, who are frustrated by the expense of the medications, their side effects, and the lack of response of the redness to them. Setting reasonable expectations for patients will go a long way toward avoiding therapeutic disappointment. The failure to explain this can lead to misunderstanding, frustration, and friction between patient and physician. Anti-inflammatory medication, whether topical or oral, does absolutely nothing for purely structural erythema or purely functional erythema. Topical brimonidine gel or even topical oxymetazoline nasal drops or spray provide a temporary paling effect.

1.2.3 The third part, the firm fibrosis

The classic "end stage" of acne rosacea is the rhinophyma, or the "drinker's nose." This is relatively rare, fortunately, and is caused by an increase in thickness of the involved tissue that is termed a *phymatous change*, from the Greek word *phyma* meaning *nodule* or *swelling* (Figure 0.33). The nose is most commonly involved, although the cheeks, forehead, and chin may sport the disorder. W.C. Fields is the actor and personality most often associated with rhinophyma, but President William J. Clinton may be a more familiar face. Alcohol intake has been suspected as a co-factor but need not be present. The true cause may (again, hypothetically) be suspected by reference to the progressive fibrosis that occurs in areas of chronic edema of the lower extremities, a component of stasis dermatitis often seen on biopsy. Some individuals may simply be sufficiently

susceptible to overproduction of such material either on their lower extremities or as a result of stasis in the dermis of the face, induced secondarily, as Prof. Marks would suggest, by the vascular damage caused by the sun, not only to the venules but to the lymphatics as well. This results in leakage of proteins and induction of a fibrotic reaction that thickens the areas under the skin in the facial area, and occurs on the lower leg due to gravity and senior citizenship. The reason why *all* patients with rosacea do *not* progress to phyma formation remains a mystery. There does seem to be a genetic predisposition, but choosing new parents is not an option in this age group.

1.2.4 Part four—ocular rosacea

If an itchy, scratchy, or gritty feeling in the eyes occurs in association with other signs of acne rosacea, then consider the diagnosis of ocular rosacea. There is dilation of the blood vessels on the surface of the sclerae (the whites of the eyes) and a swelling of the tissues around the eyes, particularly the eyelids and the eyelid margins (see Figure 0.34). This disorder does not seem to appear often as an isolated ophthalmological disease, so it seems to be truly related to cutaneous acne rosacea. The mechanism of its cause, however, is as mysterious as the cause of rhinophyma.

1.2.5 Putting it all together

While there is no denying that acne rosacea is usually associated with background redness, patients with background erythema and telangiectasia may experience redness and flushing alone. Other individuals with actinic telangiectasia may have bumps alone or bumps and pimples together, with or without phyma formation (thickening of the involved skin), and with or without ocular (eye) rosacea. Combinations of all six features are common, but real acne rosacea starts in the little oil- and hair-producing organs, the FPSUs that populate all but a few areas of our body surface.

So what is the common thread that connects the redness with the bumpiness and the little pustules? We need to go back and look at several parts of the whole, and then tie them all together.

First, we need to review what we know about the epidermal appendages that host this disorder. As discussed elsewhere, we need to use a name that is anatomically more accurate, because the follicular component plays an underrecognized role in the pathogenesis of all the acnes. These appendages have three components, so they are better called folliculopilosebaceous units (FPSUs) (see Figure 0.20) to reflect their actual anatomy.

In classic acne rosacea, there are papules and pustules just like those in some forms of acne vulgaris, but in acne rosacea there is something missing. Consider the curious lack of comedones. This is a major clue to what is going on. If you take a close look at the lesions of acne rosacea, and talk to the patients who suffer from this disorder, two facts emerge. First, the folliculopapules come up fairly quickly, and they turn into folliculopustules fairly quickly, then they burst and heal, also fairly quickly. When they do burst, there is no "core" or "plug" in the material that exits the folliculopustule. There is usually nothing visible except pus. Acne surgery (Section 8.7.1) is not needed to remove retained foreign material. The involved FPSUs do not spend months gradually building up to the point that the wall of the duct is weakened, leaks, and then ruptures as happens with acne vulgaris. Acne rosacea is different from acne vulgaris; it is quicker and shallower. Why should that be? It appears that the same processes that are acting on healthy young FPSUs in acne vulgaris have an entirely different effect on the FPSUs of patients with acne rosacea. For an explanation, we need to look back to the section on actinic telangiectasia (Section 1.2.2, "The 'Redness' Part"). What causes the telangiectases to form? Profs Marks and Kligman agreed that this was caused by damage to the support structure of the thin walls of the capillaries in the upper layers of the dermis. And what causes that damage? Ultraviolet (UV) light, specifically the damaging "superficial" UVB and the "deeper" UVA rays of wavelengths from 280 to 400 nm. This is the same ultraviolet light that damages the collagen supporting the fresh smooth face of youth. For an example, look at another comedonal disease, Favre–Racouchot syndrome. It is not common, but its presentation and location are classic examples of what too much UV light can do on the convex curved surfaces of the face. It is apparent that destruction or weakening of the support tissue, the fibrous root sheath, and its analogs (Section 0.4) allows dilation of the duct and permits development of the classic picture in that disorder. Indeed, the full descriptive name of Favre–Racouchot syndrome is "solar elastosis with comedones" (Figure 1.5).

That picture takes a long time to develop, but the physical location on the convex facial surface of the

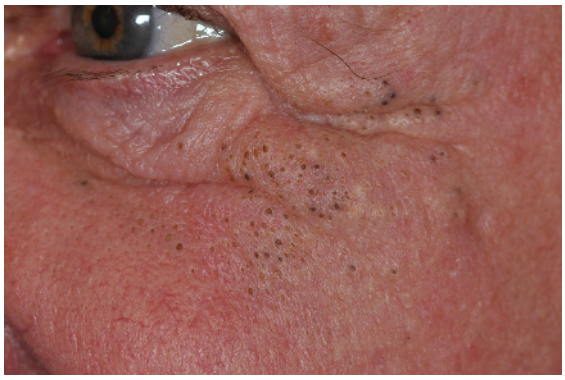


Figure 1.5 Longstanding sun exposure gradually weakens the collagen and other support tissues that wrap around and support the follicular units, allowing them to dilate. The keratin and some sebum pool in them, and some even turn dark, as on this man's cheek.

malar, orbital rim, and zygomatic areas of the face plus the associated actinic damage bear witness to the likelihood that the pathogenesis is mediated by photodamage. There is simply not enough stretch in that thin material, wrapped like a vinyl glove around the FPSU, to push these blackheads out of the weak-walled and dilated follicular canals. If you have ever had the opportunity to (sorry to offend anyone) squeeze the material out of Favre–Racouchot lesions, you will know that the keratinous mass is soft, mushy, and greasy. Its mechanism of formation relies on the weakness of the duct, the duct's expansion, and the failure of the overly compliant follicular wall to contain the mass and generate the pressure required to empty the passively filling follicular unit. This is a compliant variation of the mechanism and sequence of events that produce the hard keratinous plug in acne vulgaris.

So let's apply what we know about sun damage to acne rosacea. Look at the intimate association of the papulopustules of classic acne rosacea with actinic telangiectasia. They are basically located on top of each other. While this has led to a new classification of this disorder, the close relationship of these two features of the disorder has been, I believe, misinterpreted. *This is not just a geographic association of two different processes; it is one single environmental impact that is responsible for the two most prominent features of the disorder.*

I propose that UVA and UVB exposure is sufficiently potent and penetrating to damage the collagenous sheath that supports the wall of the follicular unit. In youth, this support structure is quite strong and forms a natural constrictive resistance. Newly formed keratinocytes and sebum press against it and are forced toward the surface by the resistance provided, so the pressure created empties the duct. That allows no time for the microcomedo to accumulate, and in youth it is unusual to have the sheath (that vinyl glove again) weakened by UV photodamage. But the rupture of the sun-weakened ducts' support does occur on occasion. Acne vulgaris flared by sunlight does occur. But, more importantly, this supports the suggestion that the reason why there are no comedones in acne rosacea and the reason why acne rosacea lesions are short-lived are pretty simple, and they are identical in both cases.

The explanation is simply that the walls of the follicular portion of the FPSU are weakened by the same UV light that caused the actinic telangiectasia. Acne rosacea pores simply lack the ability to resist the early expansion of the follicular canal, and they burst early in the game. Indeed, they burst long before the follicular canal has a chance to make a visible comedo. The break occurs at the top end of the follicle, because that is where the sun damage is the worst. Likewise, these weak follicular canal walls are so thinned that they leak easily, which leads to early activation of the innate and adaptive immune systems, so pustule formation and destruction of the upper end of the FPSU also occur early.

In short, acne rosacea is a distinct variant of the follicular occlusive disorders called the acnes. The basic cause of the lesions is identical in all acne types, but acne rosacea is localized to its specific distribution because of solar exposure. That sets the stage for the other players on the field, and that is a whole different story.

1.2.6 The inflammatory epiphenomena in acne rosacea

Each of the three acnes is distinct. The distinctions include location, time of life, the impact of environmental variables, response to therapy, lesion type, and the triggers. The eruptions of acne rosacea occur mainly on the face and in sun-exposed areas, and the general pattern is of follicular plugging, early rupture, inflammatory reaction, and healing. The reasons for the plugging and rupture are explained in this chapter, and ways to prevent, modify, and treat them will be dealt with in this volume. In addition, there are a

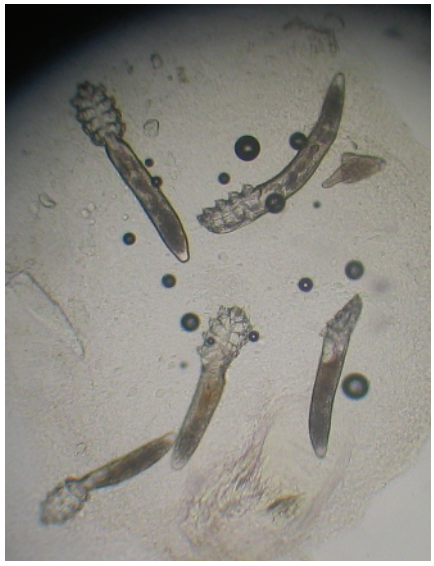


Figure 1.6 This family of adult, juvenile, and a baby Demodex mite had occupied a pustule on the forehead of a rosacea patient. The background shows pus and a keratinous plug (plus some round air bubbles).

number of variables that are important in the development of the inflammatory reaction.

Inflammation in acne rosacea, as in all acnes, is driven by the immune systems responding to materials considered a threat to the organism. As described in Section 7.1, that means that anything that should be "outside" (or above) the basement membrane is considered the enemy (see Figure 2.7). Foreign material on the surface, if it gains access through a scratch or cut, will be attacked. Likewise, anything that is caught under the epidermis (like an ingrown hair) or takes up residence in the pores (there are several organisms to consider) has the potential to stir up trouble. It is time to look at these.

There are five sets of troublemakers that occupy the follicular portion of the FPSU:

1 The classic invader in acne vulgaris is the "acne bacillus" described in Chapter 6.1. It is now known as *Propionibacterium acnes*, or *P. acnes*. It has been the target of dermatologists using antibiotics for over 60 years. For reasons that will be explained in this book, *P. acnes* does not seem to be a major player in acne rosacea.

2 The next most-blamed invader is a mite, a tiny free-living and mobile little beastie called *Demodex folliculorum* (Figure 1.6). It is a cousin of the itch mite that causes scabies. Although usually simply referred to as *Demodex*, there are about 65 species. These little fellows and girls live head-down in our open follicular openings. The males actually come out at night on the skin surface, mate, and then return to their pores. One wonders if the females also are night wanderers; otherwise, how would the infestation spread? The mites have been considered by many dermatologists over the years to be simply innocent bystanders, but there are recent clues that they are likely seriously involved in some, although perhaps not all, cases of acne rosacea [6]. One of the clues is from simply sampling the material in the little pustules that show up on patients' faces.

3 There is the interesting and increasingly likely possibility that part of the immune reactivity related to the *Demodex* is due not to the mites themselves but to their colonization by another organism, *Bacillus oleronius*. This bacterium lives in the gut of the *Demodex* and is apparently susceptible to the antibiotics that are useful in cooling acne rosacea [7]. Even more interesting, there is evidence in the serum of patients with acne rosacea of immune reactivity to antigens from *B. oleronius* [8].

4 The fourth of the five troublemakers is not a living organism. It is the contents of the follicle that are actually produced by the FPSU itself. Even in the least hairy areas of the face, tiny little hairs are usually produced by the FPSU. They may be so small that they are essentially invisible, but they show up in microscopic sections prepared from rosacea-bearing skin. In acne vulgaris, they are headed up the follicle to the surface but sometimes they can be seen tightly curled up in the middle of the comedonal plug. Just like ingrown hairs, they seem to be quite capable of causing the acute inflammation that is the hallmark of acne rosacea, and they are sometimes seen in the material prepared for KOH examination from pustule contents (Figure 1.7).

It is assumed that there are also bits of retained adherent keratinocytes in this material, and it is generally understood that loose keratin under the skin is not welcomed by the innate immune system. When an epidermoid cyst ruptures under the skin, exposing released keratin, it is sterile but it causes a massively hot and tender inflammatory reaction that is often mistaken by the unaware for infection. The resolution of such lesions, brought about by simply removing the keratin (and the germinative epithelium surrounding it), is both swift and impressive. Likewise, simply opening these little

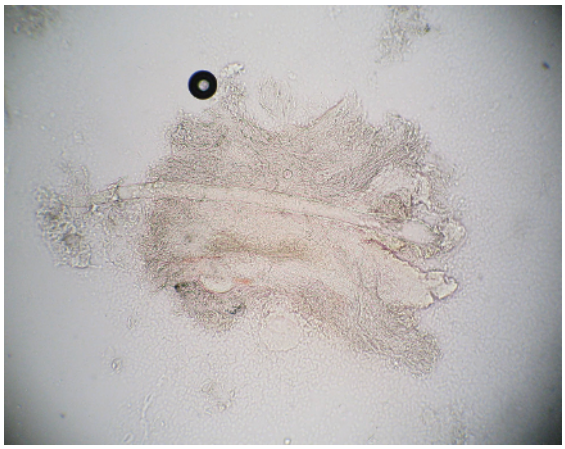


Figure 1.7 The innate immune system reacts to ingrown hairs, likely even the tiny ones like this, caught in a keratinous plug in a folliculopustule in acne rosacea.

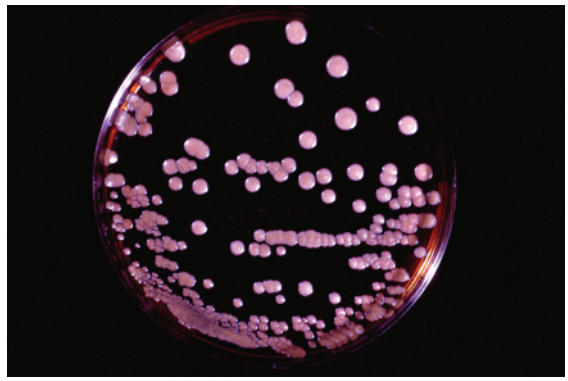


Figure 1.8 Instead of using the olive oil overlay, the nutritional requirement of *Malassezia* is met in Dixon's agar by including glycerol mono-oleate. From http://www.mycology.adelaide.edu.au/gallery/yeast-like_fungi/

rosacea pustules brings about a very quick overnight cooling of the lesions.

5 The last of the troublemakers is not well described at all in the literature on acne, but I have found it to be a factor in most of the referred cases of rosacea I treat. The fact is that the organism is also very important in the pathogenesis of acne vulgaris, a truth ignored for over 30 years, and that story is covered in the section on acne vulgaris (Section 1.1) [9]. The organism in question is the yeast *Malassezia furfur* (Section 6.2). There seems to be only one species involved in the acnes, but it is a challenge to link it with scientific rigor to any particular disorder because of three simple facts:

First, it is everywhere. Cultures of this yeast, using material taken from the scalp, its natural reservoir, are almost universally positive. It loves to live where its natural food, oil from the sebaceous glands, is present.

Second, it doesn't always cause disease. Indeed, there is a good case to be made that it is the victim, not the aggressor.

Third, it has relatives (there are 14 *Malassezia* species in all), and a close relative, *M. globosa*, appears to be responsible for the seborrheic group of disorders [10].

This trio of facts makes it very difficult to actually prove the relationship between the yeast and several cutaneous disorders. The yeast is accepted as having a causative role in tinea (or pityriasis) versicolor, and the same is generally true of *Malassezia folliculitis* of the upper back, upper chest, and shoulders, but there is ongoing discussion about its role in seborrheic dermatitis, psoriasis, and atopic dermatitis. And when it comes to acne vulgaris and acne rosacea, there is hardly a mention in the modern literature.

In making the case for *Malassezia*'s role in these diseases, a conceptual problem arises. Based on early medical school teaching that pus means infection, and pus needs to be cultured, the natural tendency of infectious disease specialists, research dermatologists, and some clinical dermatologists is to culture the pus and see what is growing. If one does that, and the contents of a rosacea pustule are sent to a general bacteriological lab, the report comes back as "no growth," "normal skin flora," "no evidence of staphylococci or streptococci," or "light growth of staphylococcus epidermidis." Despite the unconscionable cost of acquiring this essentially useless information, an exercise done in pursuit of satisfaction of the standard-of-care criteria for managing pustular infections, none of these reports is helpful.

The reason for the failure to find the culprit yeast is simple—*Malassezia* is a "picky eater." It must have fatty acids of a chain length of 12–24 carbons, or it cannot grow and thrive. These fatty acids are not present in the usual culture media used for examining putative bacterial infections. so the yeast does not grow.

If *Malassezia* doesn't grow, then it cannot be reported and so it is ignored. It is not hard to culture. All one needs to do is put a thin layer of olive oil on the surface of the standard Sabouraud dextrose agar with cyclohexamide culture medium, or mix olive oil into the agar, or use the

special Dixon's agar (Figure 1.8), but it is extra work and extra expense, and no commercial lab is generally interested in the yeast so its presence simply is not reported. About 25 years ago, my partner and I interested a local hospital lab in growing *Malassezia* (back when it was called *Pityrosporon*), and after numerous positives we (and the lab) got bored and dropped the practice. The simple fact is that the *Malassezia* yeast is everywhere. Finding it is no surprise, it adds no information, and (unfortunately) it drives nobody to consider therapy.

The other side of the coin is the difficulty in linking it with specific diseases. This is especially difficult when the disease is common (e.g., acne vulgaris, psoriasis, seborrheic dermatitis, atopic dermatitis, and of course acne rosacea). The problem stems from the fact that *Malassezia* itself is normally a simple innocent bystander. It makes no toxins, it does not invade tissue, and it doesn't destroy tissue. Mostly it just sits on the surface of the skin or goes down our follicular orifices looking for more food, the special fatty acids in the oil in the sebum made by the sebaceous part of the FPSU. At least, that is its status until something happens to call attention to its presence, and that is when the fun begins.

So what happens? We humans have an immune system (actually, two of them) always looking for trouble. And if the yeast is present in material that breaks through from the "outside" material in the follicular canal and gets through the leaks in the follicular wall and escapes into the "inside" of the dermis, the trouble starts. The body's "first responders," the innate immune system, recognize the invaders immediately and that starts a "fire drill." A whole cascade of reactions is triggered, and there is redness, swelling, pain, and heat—the classic signs of inflammation. This causes the red bump we know as a folliculopapule, and that is followed in a very short time by a folliculopustule. The reaction continues until the threat is eliminated, which generally means the pustule breaks (or is evacuated by its owner) and healing proceeds.

One problem in proving the relationship of the infection or inflammation to the yeast is the difficulty in satisfying "Koch's postulates." These postulates comprise a set of four rules that were set up in the nineteenth century to "prove" the causal relationship of an infectious organism to the infection it causes:

1. The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms. The problem here is obvious; *Malassezia* is everywhere, but not all hosts suffer the disease.
2. The microorganism must be isolated from a diseased organism and grown in pure culture. This is easy to do but is not often done.
3. The cultured microorganism should cause disease when introduced into a healthy organism. The problem here is that the microorganism is already introduced to all of us. Some of us have trouble; most do not.
4. The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent. Again, we all wear the yeast, so this is pointless.

In fairness, Koch's rules have been bent in many directions over the years and are now really of historical interest only, but I still am called to explain this to disbelievers at clinical meetings on a regular basis. It is really best to consider the reaction we see as being more like an allergic contact dermatitis rather than an infection. As an analogy, just about everybody wears jeans at some point, but only a very few of us are allergic to them.

And that is what is happening here—some of us are actually allergic to the yeast. So the problems caused by the inflammation are not caused by the yeast attacking us humans; rather, we humans have immune systems that are attacking the yeasts. We are suffering from "friendly fire." I've seen dozens of women over the years with acne rosacea that is triggered in part by yeast, and there is one story I hear over and over again that tells a tale and reinforces (but does not prove) the theory. Almost invariably, I would say over 90% of the time, if you ask a woman with *Malassezia*-associated acne rosacea if she has ever had problems with vulvovaginal yeast, the response is "Yes, once or twice, many years ago, but not recently." These women, I believe but cannot prove, have a very well-developed adaptive immune response to yeast. That response was triggered years ago as a result of vulvovaginal exposure to *Candida*. That exposure has been sufficiently effective in providing a defense against further episodes of *Candida* that there have been no further problems from the *Candida*, which is *Malassezia*'s cousin. That exposure and response also seem to set up a cross-reactive sensitivity to *Malassezia*. This cross-reaction is strong enough to show up as an itch (likely immunoglobulin E mediated)

but is not strong enough to eliminate the *Malassezia* from the skin surface, or from the pores.

It is worth noting that women who have had vulvovaginal yeast infections are very quick to recall how itchy the problem was. Consequently, if a woman with rosacea reports that itch is a part of her problem, then *Malassezia* is almost certainly the major troublemaker down in her pores.

One caution is in order here: women with *Malassezia*-mediated acne rosacea have often had the condition for so long that they do not even realize they are itchy. They often will have simply scratched the tops off their little pustules, usually without even realizing it (or admitting it). This often occurs at night, during twilight sleep when they really are not in control of their wish to scratch. But the history of itch or the presentation with excoriated papules, even when itch is denied, is satisfactory evidence of likely *Malassezia*-related inflammation. The differential diagnosis where itchy papules exist is *Demodecosis*, so that presents us with two treatable conditions—more on how to do that treatment later.

The fascinating thing is that these women (and a few men as well) will not be aware of the itch until after successful treatment has been completed. That is why I call *Malassezia*-induced inflammation the Joni Mitchell disease—because of the line "You don't know what you've got 'til it's gone" in her famous song "Big Yellow Taxi." It is a part of rosacea that is actually made worse by the usual antibiotic treatment and generally goes both unrecognized and untreated.

1.2.7 The "acne rosacea" versus "rosacea" controversy

This confusing change in the name occurred when an Expert Committee suggested a change in the criteria for the diagnosis of rosacea. A new classification, erythematotelangiectatic rosacea, was added [11]. The criteria for making the diagnosis were changed so that anyone with persistent redness of the center of the face (central facial erythema with or without telangiectasia) fits this diagnosis. This is true even though they suffer from nothing more than the sun-induced changes once known simply as "high colour" in the British literature and as rosy cheeks in everyday writing. This tendency of the convex areas of the face, particularly the youthful "apple" of the cheeks, to accumulate sun damage is a very natural aspect of life, a point recognized by artists over the centuries. Surely, all the rosy-cheeked cherubim and seraphim and the Infant Christ Himself depicted by artists over the past 500 years were not all afflicted with rosacea!

If you would like to explore the nomenclature problem further, you can see the Expert Committee's work at http://www.rosacea.org/class/classysystem.php. My objection to it, and the Committee's response, comprise Appendix A.

In this book, acne rosacea is one of the acnes. And *rosacea* is an adjective, not a disease.

1.2.8 Summary

In summary, where there are numerous dilated blood vessels caused by sun damage, it is proposed that there is also damage done to the supporting structure of the FPSUs in the same area. This weakening of the wall of the follicular duct preempts the development of visible comedones, predisposes to easily ruptured folliculopapules and folliculopustules, and sets the stage for the immune-mediated inflammation that characterizes the rosy clinical picture presented by the combination of actinic telangiectasia and acne rosacea.

1.3 Acne inversa (formerly hidradenitis suppurativa)

The French surgeon Verneuil described a disease in 1864 that he named *hidradenitis suppurativa* (HS), thinking that it was a disorder of the apocrine sweat glands. Subsequently it was realized that the primary area of involvement was, as in acne vulgaris, in the follicular portion of the FPSU. The term *acne inversa* (AI) was first applied in 1991 [12]. That paper set the ground rules for the use of the term at the time.

> Acne inversa is a chronic inflammatory disorder of sebaceous follicles and terminal hair follicles and is one type of (the) acne diseases. The pathogenesis of acne inversa is identical with that of the other types: Hyperkeratosis of the follicular infundibulum leads to a comedo. Bacterial infections result in a rupture of the follicular canal followed by a granulomatous inflammatory reaction with abscesses, panniculitis and draining sinuses.

Although a shift seems to have been gradually occurring recently, particularly in Europe, the newer term AI has not been fully accepted by all workers in the field. This is partly because many of us are traditionalists; partly because some of us are too lazy to think about

new names, even when the old name has lost relevance; partly because patients, most physicians, and the medical literature are more familiar with the old term; and partly because AI is a term that suggests that the condition occurs in areas that are upside down (inverted) from the usual location of acne—a concept that doesn't relate well to reality. There is, however, a new and scientifically accurate reason to support this term. That discussion will come a little later.

For now, I am using the term *acne inversa* because it fits with the unitary concept of this book—the concept that all three acne conditions are indeed variants of a single, if somewhat complex, disease process. The differences among the acnes are produced by three factors:

First, they occur in different, but sometime overlapping, geographical areas of the body.

Second, they affect different types of FPSUs.

Third, they actually involve different areas of the FPSUs.

AI has been described, under its synonym *hidradenitis suppurativa*, as an orphan disease. That implies that it has been abandoned by its parents. In day-to-day practice, unfortunately, it is more often than not abandoned by its "foster parents," the physicians and surgeons who should have been caring for it. It is not taught in many medical schools, is poorly taught in most dermatology training programs, sometimes dealt with using the most heavy-handed surgical techniques conceivable, and is regularly ignored or misdiagnosed (or both) by family physicians, emergency room physicians, plastic surgeons, gynecologists, infectious disease physicians, and even our dermatology colleagues. There are dermatology textbooks in which it cannot be found. It is often so completely serially ignored by members of the medical community that the patients themselves, having visited a number of physicians with no results, abandon both hope and care. They hide, lose jobs, lose social contact, lose loved ones, give up on therapy, and fade away from their physicians. They show up in our offices, in urgent care, or in the emergency room, not out of hope for a cure but only out of despair because of the pain, ashamed of their wounds, and embarrassed by the inescapable odor that often accompanies unpredictable discharges.

But there is now some hope. A small group of dedicated researchers and clinicians from around the world has renewed interest in the disease. In 2006, they were cajoled into attending an international meeting by a persuasive Californian suffering from the disorder. Indeed, she helped finance the event. Hosted and chaired by Professor Christos Zouboulis in Dessau, Germany, the group is still in touch, has met once more in San Francisco, and is presently reorganizing as separate but cooperating North American and European Foundations. (See http://www.hs-foundation.org.) Both are working at various aspects of the disorder. At the forefront of the slow but steady push forward is the senior author of the first book in 50 years to deal exclusively with "Hidradenitis Suppurativa," Professor Gregor Jemec of Copenhagen [13].

The disease starts with the same early plugging of the follicular portion of the FPSU that occurs in acne vulgaris. The expanding plug causes gradual dilation and eventually a rupture of the fragile wall of the unit. This in turn leads to an explosion of inflammatory activity but, instead of pushing up to the surface, discharging pus and the keratinous plug, and then healing like most boils and acne vulgaris lesions, the inflammation travels horizontally and over time it creates gel- and pus-filled sinuses under the skin that grow sideways and eventually erupt to the surface. These inflamed and interconnected sinus tracts, initially sterile, may then become secondarily infected, adding to the inflammation and causing swelling, scarring, drainage, pain, odor, and a great deal of patient distress. This is most common in areas that are under pressure from tight underwear, close-fitting clothes, belts, brassieres, bra straps, and the pressure of sitting and other local trauma. It can also occur in areas where regular acne vulgaris is common, on the face and neck and behind the ears, in areas that are not at all "inverse." Patients with this disease who develop facial acne have a deep nodular and scarring variant of resistant acne that is very difficult to treat.

The way this disorder progresses brings us back to the name of this condition. In this variant of acne, the leaks and ruptures that lead to all the trouble occur right next to the *deepest part* of the *follicular* unit of the FSPU. Anatomically, this is where the sebaceous glands originate. They are attached at the lower end of the follicular tube, forming the sebofollicular junction (Figure 1.9). This appears to be the site of the weakness that leads to the leakage and eventual rupture of the wall of the FPSU [2]. That breach in the wall allows the contents to leak, and that starts the inflammatory reaction (Figure 1.10). That reaction can be very intense, causing increasing and self-perpetuating damage to the area and

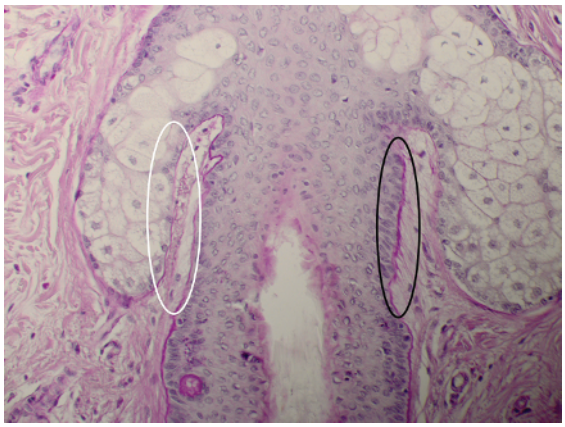


Figure 1.9 Note the variation in the thickness of the PAS+ (periodic acid–Schiff positive) support material, 2–3+ on the outside of the pilar unit (black oval) and 1/2 to 1 1/2+ on the inner aspect of the sebofollicular junction (white oval).

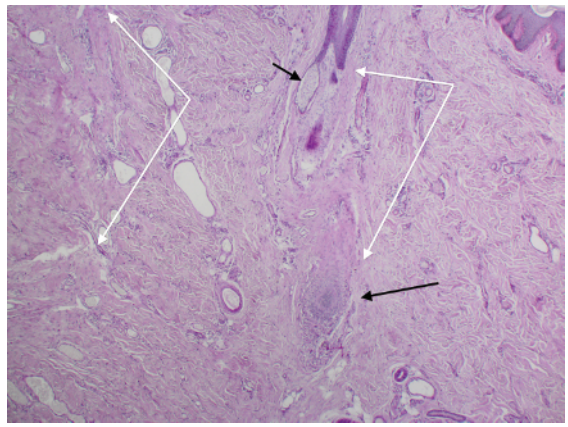


Figure 1.11 Double white arrows show areas of destruction, with smudged scarred collagen. The short black arrow shows a diminished residual sebaceous unit. The long black arrow indicates a pilar papilla under destruction.

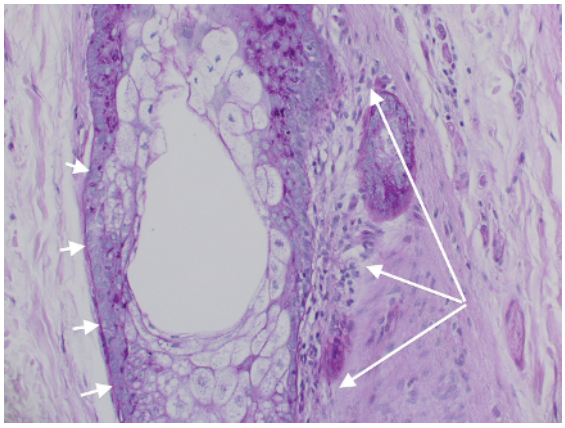


Figure 1.10 The short arrows show periodic acid–Schiff (PAS) 2+ and no inflammation; the long arrows show PAS 0–1+ and active inflammatory infiltrate.

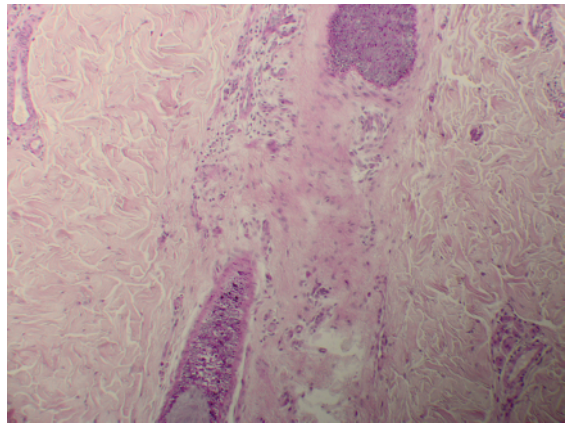


Figure 1.12 The uninflamed healthy collagen on either side of this half-destroyed sebofollicular junction provides evidence of the specificity of the inflammatory attack. No sebaceous gland remains.

destroying the sebaceous glands and the pilar unit in the process (Figures 1.11, 1.12, and 1.13) [14].

This initiating chain of events occurs at the most *inverse* part of the follicular portion of the FPSU. It appears likely that this physical defect and weakness is in this *inverse* location whether the involved duct is present in the classic groin and armpit areas of AI or on the "non-inverse" face and neck. It is for this reason that I have accepted and will use and promote "acne inversa" as a reasoned, and reasonable, name for this variant of acne. Accepting this explanation brings a degree of logic to the name of the disease, correcting a misnomer that has existed since the inaccurate assignment of responsibility to the "sweat glands" by Verneuil well over a century ago and specifically to the apocrine sweat glands by Brunsting in 1939 [13].

Note that there is no destruction or even inflammation directed at the apocrine glands themselves. They stand unharmed in a sea of inflammation (Figure 1.14). This disease was never a hidradenitis; it has always been a variant of acne. Nor has it ever been a disease that started in the pilar or sebaceous portions of the FPSU, hence the need for the new anatomic and histologic

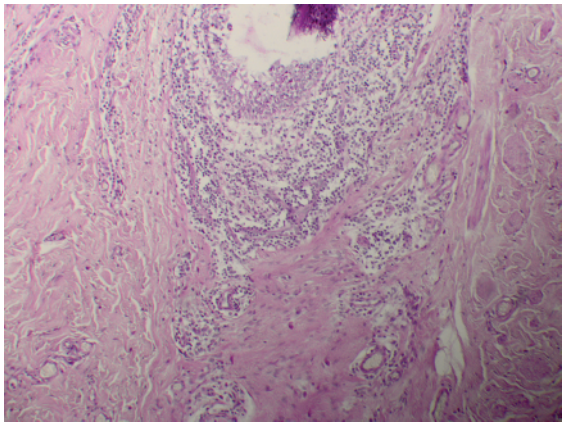


Figure 1.13 The outline of the residual parts of the pilar unit is just barely visible.

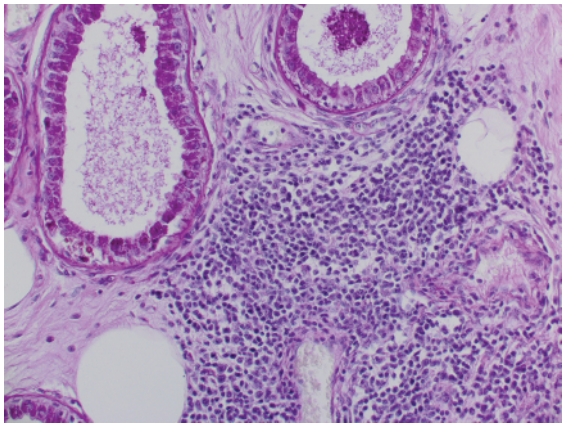


Figure 1.14 Despite the intense inflammatory activity nearby, the apocrine glands show no structural damage.

terminology, recognizing the sebofollicular junction of the FPSU as the site of the problem.

In summary, acne inversa is a disorder of follicular keratinization characterized and caused by plugging of the follicular portion of the FPSU and leading to rupture of the *inverse* end of that structure at the sebofollicular junction.

No matter where it happens to be on the skin surface, acne inversa really *is* acne turned upside down.

1.3.1 Before the rupture, where and why?

If you haven't read the section on the influence of solar damage on the development of acne rosacea, it is time to back up and read it now (Section 1.2). You need to know what is happening in the top end of the follicle in sun-exposed FPSUs.

So having absorbed that lesson, give some thought to what happens to the follicular support tissue in AI/HS. Think about the effect the sun has on the involved areas. Could it be that the acroinfundibular part (the top end) of the follicles in the intertriginous and genital areas are naturally quite strong, tight, and easily plugged partly because they get NO sun exposure? Suppose we take a giant conceptual leap of faith forward at this point. Could it be that the effectiveness of laser light in managing AI/HS (see Section 8.8.2) is partly dependent upon damaging the support tissue of the upper part of the follicle and allowing it to empty instead of plugging up and rupturing? Of course, there is no proof of this yet, but I think it certainly would be worth a careful scientific look. There are several other links to light (or the lack of it) in this problem—more on that in due course (see Section 8.8.1).

1.3.2 After the rupture, what next?

The events triggered by the rupture of the duct are numerous, interrelated, complex, difficult to treat, destructive, self-perpetuating, and only partially understood. Much of what we see is the result of inflammation caused by the immune system's reaction to material that was in the plugged pores. If you have ever had an ingrown hair, you know that the swelling and tenderness are out of proportion to the size of the hair. Even more important, if the hair is plucked out of the pore or even just flipped free from being trapped (without being plucked), the inflammation goes away almost immediately. No antibiotic is needed.

Why? Because this is an *inflammation*, NOT an *infection*. No bacteria or yeast are required to cause the redness and swelling. This is the kind of inflammatory reaction that is caused by our *innate immune system*, and the reaction may be later augmented by our adaptive immune system. See Sections 7.1 and 7.2.

1.3.3 So what invaders are important in acne inversa?

Just as in acne vulgaris, the contents of the follicular portion of the FPSU make up the foreign materials that set off the inflammatory reaction. Keratin, which is what makes up our hair and nails, the surface of our skin, and the lining of the follicles, was designed to be "on the outside." When keratin is sitting in the pore as a hair or a

duct-lining keratinocyte, there is no problem, but if the hair is "ingrown" into the dermis, the innate immune system under the epidermis recognizes it almost immediately and the inflammation starts. But think how amazingly fast the inflammation goes away when the ingrown hair is flicked out of its little tunnel under the epidermis (the top layer of the skin) and onto the surface. No foreign material in the wrong place = no inflammation.

The same thing happens with the keratin of ingrown toenails. It is a bigger procedure, but removing the part of the nail that has become ingrown, or surgically cutting away the overhanging skin tissue, leads to fairly quick relief. This is true even when prolonged use of antibiotics has proven useless. There is a lesson there. No foreign material in the wrong place = no inflammation.

Keratin from the burst follicular portion of the FPSU is instantly spotted by the innate immune system. It causes almost immediate inflammation [15]. We recognize the swelling that shows up around the follicle as an acne vulgaris folliculopapule or as the hot painful early nodule of AI/HS. If the inflammation proceeds to the point that pus is formed, a folliculopustule (pimple) has occurred. The point is that keratin, which is normally our friend, protector, and crowning glory as our skin, nails, and hair, is the enemy when it gets caught where it shouldn't be. If a simple epidermoid cyst on the back bursts, a huge reaction to the keratin occurs, even though the keratin is sterile and may have been sitting quietly protected in the intact cyst sac for decades. All of the antibiotic in the world won't cure that reaction, because the inflammation is NOT caused by infection. Real infected cysts are really rare. But inflamed epidermoid cysts (often misnamed *sebaceous cysts*) are very hot, very sore, and usually very sterile. Total evacuation of the keratin and the entire leaking epithelial sac that surrounds the keratin mass is curative. No foreign material in the wrong place = no inflammation.

If the immune system's recognition of keratin was the only thing causing the inflammation, one could simply empty the keratin and reactive pus and expect healing. But in AI, we have a problem. The problem may be fairly easy to look after if only one fresh new hot spot has occurred, but there may be masses of active spots.

Let's take a look at a solitary inflamed AI/HS nodule first. Remember, the process is upside down in the follicular structure, with the trouble at the bottom or the side of the follicular structure. Just emptying out the keratin and the pus with a stab incision and a squeeze will give temporary relief—*but it leaves the damaged follicle behind.* That means the whole process can start all over again. So what is the answer? It is so simple that I wonder why nobody has thought of it before. All that needs to be done is a simple procedure using a biopsy punch, basically a sharp and disposable little instrument that works like a round cookie-cutter. We usually use these in dermatology to do biopsies and they come in various sizes. A 4, 5, 6, or 7 mm biopsy punch can be used to take out the whole plugged and leaking inflamed FPSU. It is really quite simple to do and, because local anesthetic is used, it is then possible to aggressively squeeze out and debride any residual pus and keratin (Figure 1.15). The wound is sealed with a chemical coagulant bleeding-stopper (ferric chloride is preferred) and left open with nothing but a petrolatum dressing, to leave a small scar (Figure 1.16). This works well on fairly small, early, solitary lesions of AI. For painful spots

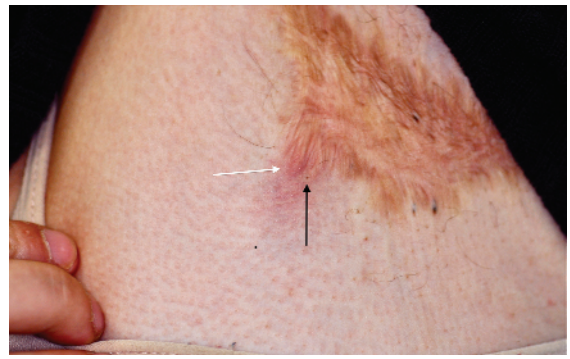


Figure 1.15 Note the red tender area (white arrow) with no comedo and the tombstone comedo (black arrow) next to it.

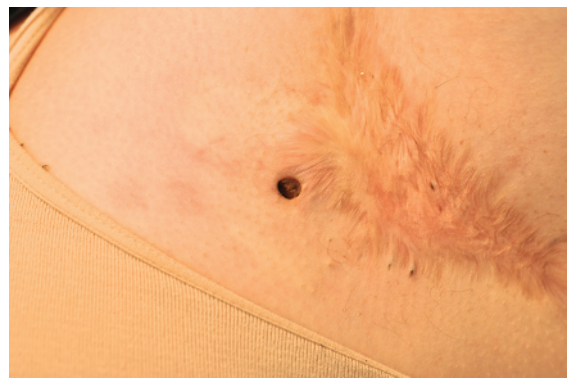


Figure 1.16 Excision site placed to remove both inflamed lesion and tombstone comedo.

in the areas under breasts, under bra straps, along panty lines, and on buttocks, the pain relief is a joy. (See Section 8.7.2.1 for full operative details.)

A much more involved problem occurs when the lesions are multiple or have been untreated for too long. This happens far too often and is generally caused by delays in diagnosis, misdiagnosis, inadequate treatment, inadequate prevention, and inappropriate incision and drainage (I&D) procedures in doctors' offices, operating rooms, urgent care facilities, and emergency rooms around the world. It is sad but true that AI/HS is so commonly mismanaged that mismanagement is the de facto standard of care. Why does this disease cause so much trouble, and what is the best way to treat it?

One needs to understand that, from a practical point of view, there are three ways to treat AI/HS surgically. The first is described above, punch ablation or debridement and mini-unroofing of a single complete inflamed FPSU. It is appropriate for solitary lesions and works best in new lesions. The second is the unroofing technique, described below, which is useful in managing the older and well-established localized single or multiple nodules and sinuses. These *can* be rendered quiet with aggressive medical care prior to the unroofing, but the medical care is at best a temporary substitute for, or preparation for, the surgical unroofing. At the other end of the line is the need for the third option, full surgical excision of the entire involved area with appropriate margins. This may be the only way to manage the massive, draining, malodorous, scarred, and sinus-ridden involvement of the axillae, groin, perineum, buttocks, or genitals (or, even worse, combinations of these).

The Hurley three-stage classification that is used in HS/AI is based upon the number of lesions, the number of areas, and the extent of the involvement of the entire patient rather than the individual lesion types. While the Hurley stage gives us a classification of the severity of the disease in general, it is only a rough therapeutic guide. Thus, even the worst Hurley Stage III patients may benefit from selective use of all three of these surgical techniques, depending upon the age, type, activity, and location of the lesions. And the preventive medical dietary and behavioral changes must continue in place for years, if not for a lifetime. (See Chapter 8.)

So what does one do for patients who have large nodules and abscesses that involve more than one FPSU but are not bad enough to need the full surgical excision and repair? Basically, one must recognize first that what we are dealing with is NOT primarily an infection, even though there may be some secondary infection. The inflammatory chaos that the patient presents to the physician is due to a massive innate immune response to retained keratin and other debris. It is in essence an out-of-control "ingrown hair" reaction that has "gone nuclear." It may sound simplistic, but Grandma was right; if you get the core out, then everything settles down. Even the ancient Romans knew that, and gave us the instructions "*Ubi pus, ibi evacua*," Latin for "Where there is pus, evacuate it." The debris must be removed and the wound provided with the best conditions possible for healing. Removal of debris is called *debridement*, and the only way to fully debride that material from under the skin surface is to remove the entire roof from the nodules, sinuses, and abscesses, and clean them out (Figures 1.17 and 1.18).

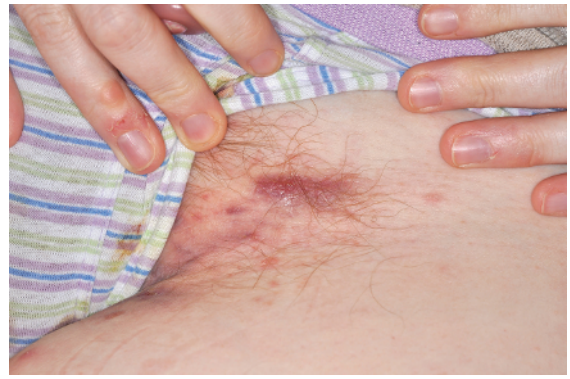


Figure 1.17 This is actually the first of several lesions, some of them communicating, that involve this left inguinal crease.

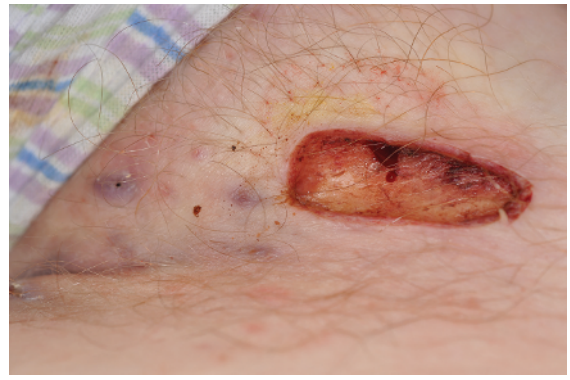


Figure 1.18 A simple oval cut with scissors cleared the area nicely. Further extensive work was needed to the left, inferomedial to this lesion.

Unroofing is remarkably simple compared to the major surgery used for Hurley III. It can usually be done in the doctor's office, the outpatient clinic, or the emergency room. No hospital admission is needed, and there are several other advantages. Time off work is usually minimal. (See Section 8.7.2.2 for full operative details.)

1.3.4 What makes this disease behave so much worse than acne vulgaris?

The major difference, recently demonstrated, is the location of the break in the follicular wall and the sequence of destructive events that follow. There has been a series of papers published recently that tell us more about this area than we ever knew before. The important features are the following:

There is apparently a defect in the support structure of the FPSU, with no support (or very weak support) right at the spot where the sebaceous glands originate from the follicular unit, just above the upper level of the pilar unit [16].

Inflammation appears in areas where the support structure is thin or missing. That pinpoints the area where the breakdown occurs.

The inflammation consists of all the regular series of inflammatory cells one would expect [15].

The sebaceous glands have been shown to almost disappear, blown off by inflammation [14].

In areas where the sebaceous glands are gone, there is visible inflammation and scarring. The destructive inflammatory process leaves behind little stumps where the sebofollicular junction previously existed.

Just below the sebofollicular junction in the pilar unit of the FPSU is a group of cells that produces a visible bulge, so it is called the bulge region. This is a segment of the pilar unit between the attachment site of the arrector pili muscle to the pilofollicular structure below, and the beginning of the sebofollicular junction at the isthmus above (Figure 1.19). The arrector pili muscles make the hair on the back of your arms stand up in a chill. More importantly, that bulge area is where stem cells come from.

The main job of these stem cells is to make sure the hair follicle and hair root are stimulated to grow and replace themselves, to be sure that the FPSU continues to grow hair even if it is damaged, and to repair all portions of the FPSU if and when damaged. Thus,

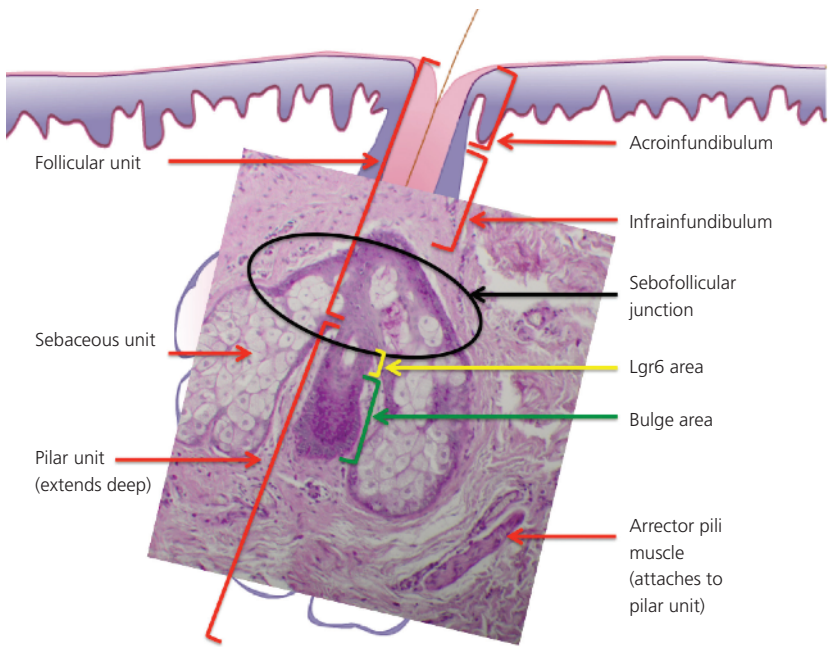


Figure 1.19 The stem cells that form the bulge migrate from the deeper part of the bulge upward toward the sebofollicular junction, and their characteristics and potentials change as they move "north." The stem cells bearing the Lgr6 marker (in yellow) are, at the time of writing, the best candidates for producing the epithelialized sinuses that represent the FPSU's attempt to heal.

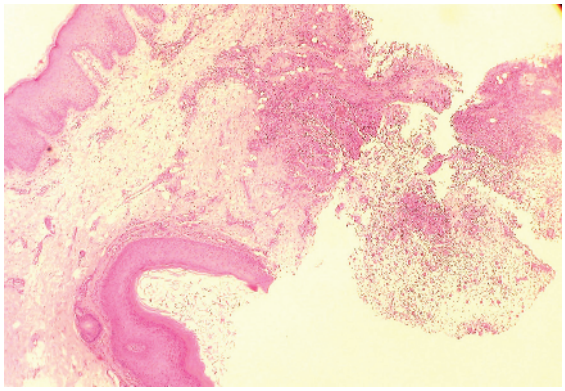


Figure 1.20 This biopsy was taken early in the development of a single lesion, and was done with a 6 mm punch. The material recovered contained a localized area of gelatinous material at the lower right in addition to the fragment of exploded FPSU and the intense inflammatory activity located more superficially.

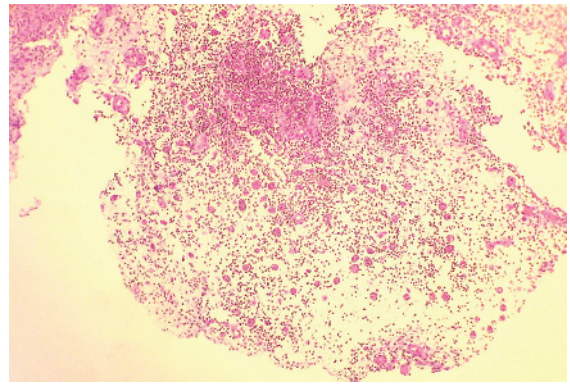


Figure 1.21 Scattered throughout this loose gelatinous matrix are several cell types, including keratinocytes, inflammatory cells, evolving new capillaries, and about 20 little round bundles of cells that are suspected to be "activated keratinocytes," likely of stem cell origin, likely from the Lgr6+ population, and the likely source of the small structures in Figures 1.23 and 1.24.

stem cells can turn into all sorts of cells. When the sebofollicular area ruptures, the break occurs right next to the area occupied by the stem cells, and the closest stem cell variety to the sebofollicular junction is the Lgr6 series. The inflammation appears to allow (or perhaps stimulates) the stem cells to break loose, and they float off into the surrounding mixture of inflammatory cells and fluid. A population of "stem-like cells" has been identified in this inflammatory material by Gniadecki, and it is hypothesized that they are the source of the characteristic material found in AI/HS lesions [17].

These stem-like cells and accompanying inflammatory (and reparative) cells exist in a gelatinous soup. It is rich in nutrients because the body makes sure that the environment for healing is as good as possible. The hormones needed to stimulate the growth of hairs and indeed the entire androgen-driven FPSU are surely present. The stem-like cells appear to be quite capable of living life on their own, and newly created islands of actively growing and dividing cells appear (Figures 1.20 and 1.21) floating in the gelatinous mass. Indeed, the "stem-like" cells are suggested to initiate the growth of these islands by changing themselves into more specialized structures, which is exactly what stem cells are programmed to do. All this needs proof, of course, and the technology is improving every day.

In summary, it is beginning to look like AI/HS is caused by the coincidental physical proximity of a congenital weakness in the follicular wall right next to the congenital strength of the stem cell line. Quite the coincidence!

When these islands come together in the invasive proliferative gelatinous mass (IPGM), genetic programming appears to get to work. Because the source of these activated keratinocytes appears to be from stem cells and stem cells are tasked to perpetuate and repair the folliculopilar structure, they attempt to create a hollow structure whose first product is a protective PAS+(periodic acid–Schiff positive) basement membrane equivalent, most likely fabricated by the basal cells it is protecting on the outside, and lined on the inside, as these structures mature, with squamous epithelium. This presumed genetic stimulus, carried by the stem cells, almost certainly pushes the little round collection of cells to become the little islands (Figure 1.22) that continue to grow and coalesce, making groups of hollow structures that join together (Figure 1.23). This seems likely, barring another explanation, to be the source of the extensive network of interconnecting sinuses that extend under the skin in AI/HS (Figures 1.24, 1.25, and 1.26).

Importantly, there is no histological evidence that these epithelialized sinuses originate as down-growths from the plugged and ruptured follicles, as has been suggested. To the contrary, the residual upper part of the FPSU retires from the field of battle and becomes the receptacle in which the open tombstone comedo occurs.

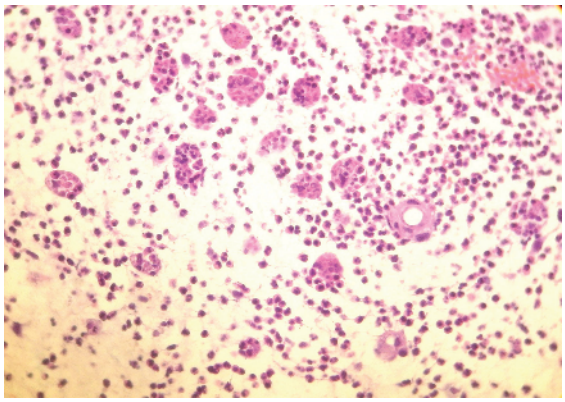


Figure 1.22 The difference in morphology between the newly formed capillary (right central) and the other little round bundles of cells is apparent. Marker studies to accurately identify these structures are under way.

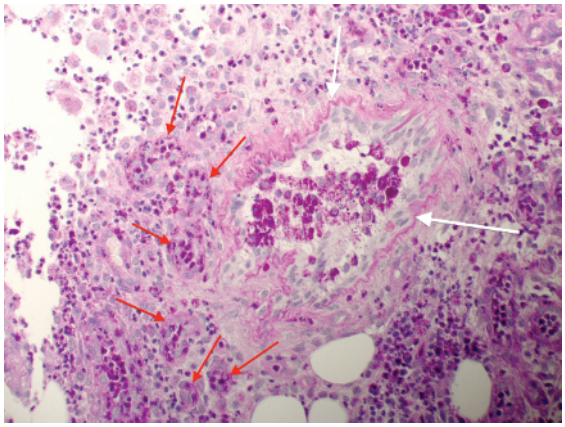


Figure 1.23 The central structure is apparently the precursor of the sinus tracts. Its first chore appears to be the fabrication of a protective barrier of PAS+ (periodic acid–Schiff positive) material. This is obvious centrally (white arrow), but on closer observation one can see several other younger structures (likely evolved from the "little round bundles") showing faint early PAS+ barrier development (red arrows).

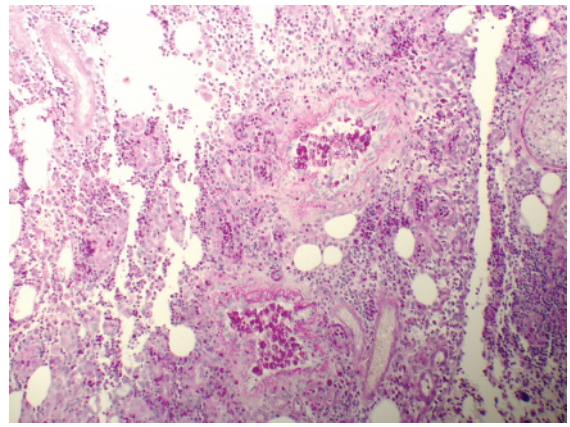


Figure 1.24 The structure appears to be no accident. The remarkably PAS+ (periodic acid–Schiff positive) cells in the center are a feature of the pilofollicular structure. See Figure 1.12 and the bulge area in Figure 1.19.

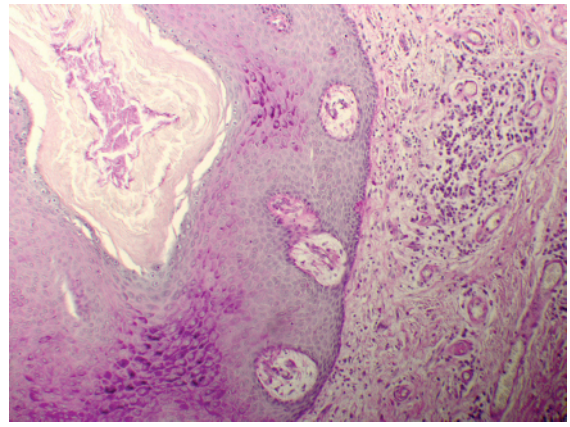


Figure 1.25 The protective PAS+ (periodic acid–Schiff positive) layer has allowed coalescence of several of the primordial sinus structures. Note the outer PAS+ material, the basal cell layer, the acanthotic "epidermoid" sinus lining, and the immature but recognizable laminated keratin, all under development.

The proliferative gelatinous mass in which 'stem-like' cells do their growth magic is a unique material, not well described in the literature. Histologically, one observes areas of acute and chronic cell inflammation nearby, but the gel is relatively sparsely populated. The initial accumulations of epithelioid cells do not seem to attract much in the way of inflammatory activity. They seem to live charmed lives and are apparently avoided by both immune systems. The new structures remain undisturbed during their formation and early growth. This may be due to preferential protection conferred by their status as stem cell products, or due to their PAS+ outer layer. As these structures mature, enlarge, and rupture, they are doubtless recognized eventually as foreign material. They are then responsible for turning on the innate immune system and all its inflammatory mediators, in the same way as ingrown hairs under the skin do. We are, however,

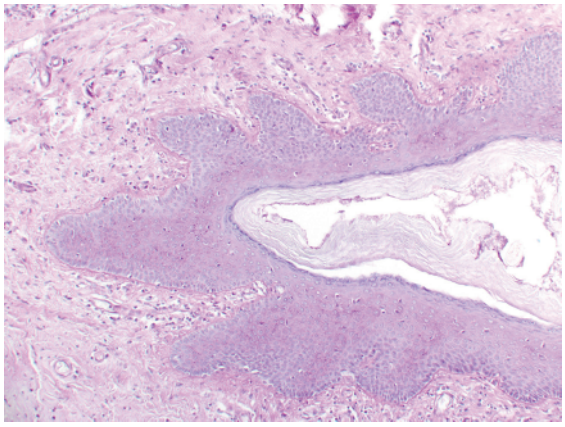


Figure 1.26 The PAS+ (periodic acid–Schiff positive) layer is better developed, now a healthy and protective 3+; the epidermoid lining is better defined; a stratum granulosum has developed; and the keratin is truly laminated.

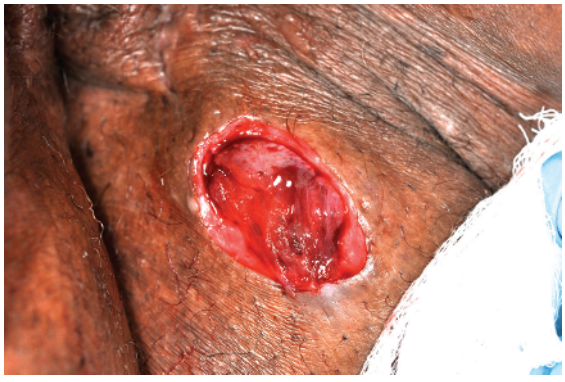


Figure 1.27 This indolent lesion had been present for months. Note the invasive proliferative gelatinous mass (IPGM) at the base.

fortunate that these stem cell islands never seem to organize to produce terminal hairs, a missing complication for which we can be very thankful. Nor do they seem to produce any sebaceous glandular material, restricting themselves to attempting to reconstitute the follicular unit.

Despite the severity of the inflammation, it must be emphasized that the IPGM (Figure 1.27) caught under the dermis and progressing laterally is not infected, although it is certainly inflamed and very uncomfortable. More importantly, when one opens a nodule by unroofing it, pus is released only if there is active inflammation, due to either the foreign body effect of

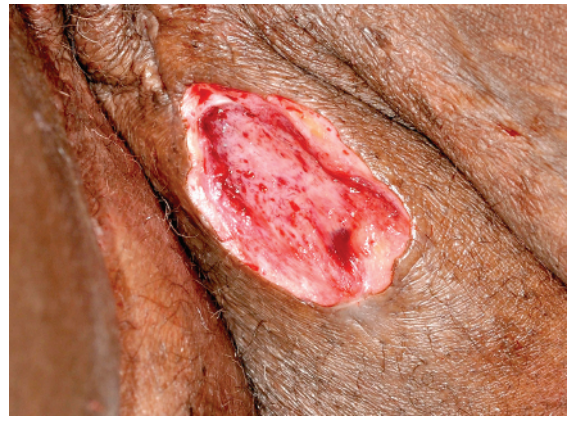


Figure 1.28 Clean healthy base. This tissue wants to heal; it just needs to be given the opportunity. Ferric chloride and petrolatum normally heal such wounds in about 10–14 days.

the trapped material or secondary infection. Instead, the proliferative mass is revealed as amorphous gelatinous tissue that can often be simply curetted or wiped away, leaving clean dermis and subcutaneous fat that heals quickly with topical petrolatum alone, normally needing no antibiotic (Figure 1.28). This is not the pink to bright-red bleeding vascular matter of which granulation tissue is made. Nor is it the "slimy" intraductal material that comprises bacterial biofilm [18]. IPGM is a unique gelatinous substance that populates almost every chronic AI nodule. It is both the cradle and the royal jelly of the sinus tracts. It is another feature of AI that warrants much more investigation.

1.3.5 So what can one possibly do to settle down all this inflammation?

There is to date no known way to dissolve the IPGM by taking oral medication, or by injecting intralesional steroids or other anti-inflammatories. It is actively growing tissue and is very healthy. It appears to be spawned by fresh stem cell activity induced to repair the damaged follicle. It produces, and provides a matrix for the development of, a structure composed of well-defined collagen and glycoprotein-based supporting material. This material supports a brand new and healthy basal cell layer (I suspect this is a cooperative effort between the basal cells and IPGM-resident cells, likely fibroblasts) and gives the sinus tracts protection from the destructive activity of the inflammation.

The inflammatory component can be cooled in several ways, but usually only temporarily.

1. *Steroids*: The classic use of prednisone orally, the regular and repeated use of intralesional triamcinolone acetonide, and the occasional use of intramuscular triamcinolone have all shown variable effectiveness against individual lesions and areas of involvement.
2. *Antibiotics*: Over the years, the most popular anti-inflammatory medications have been the tetracycline family of antibiotics that just happen to be very efficient anti-inflammatories as well. Tetracycline (no longer inexpensively available in the United States), minocycline, doxycycline, and lymecycline have all been used, and other regimens have included clindamycin and rifampicin (alone and in combination). The polyantibiotic approach has recently been escalated to include a troika of very potent antimicrobials—rifampin, moxifloxacin, and metronidazole combined [19]—each of which in its own right has significant anti-inflammatory activity. A novel antibiotic monotherapy using intravenous ertapenem, which is claimed to have no such anti-inflammatory activity, has been shown in a limited early series to have similar results. Long-term follow-up is not yet available.
3. *Nonsteroidal anti-inflammatory drugs (NSAIDs)*: While these have been used, their effect is unpredictable and episodic unless used in doses that otherwise threaten health.
4. *Narcotic analgesics*: These are sometimes necessary postoperatively or for short-term management of painful nodules. We have seen a few enterprising drug seekers who take no interest in any management other than for their pain, which they contend, of course, is unrelenting and unresponsive to anything but the requested narcotic of choice.
5. *Biologics*: The demonstration that tumor necrosis factor alpha (TNFα), interleukin 23 (IL-23), IL-17, and innumerable other cytokines are involved in the inflammatory reaction of AI/HS is no surprise—where there is inflammation, one will find inflammatory mediators. Ever more potent, ever more specific, and ever more expensive, the "biologics" do work in the short term to cool the inflammation. While significant success has been achieved in cooling parts of the inflammatory process, the search for the magic bullet, the one medication that will settle everything down, continues. None has yet produced a lasting cure of AI, but the inflamed tissue can be significantly cooled to the point that surgery is easier on both the patient and the surgeon. Long-term reliance on these drugs for maintenance therapy threatens both the bank account and the health of patients relying on them.

Knowing, as we do now, that all these anti-inflammatory weapons are usually ineffective (there are occasional exceptions) in the long run, what is the option? One needs to remove the substances causing the inflammation and prevent more from forming. And the earlier this is done, the better the result.

As a case in point, consider the bright young woman who presented as I was writing this chapter. Imagine how this painful, draining, and smelly involvement of her vulva interferes with her everyday life as a busy and intelligent college student. Her love life? I did not embarrass her by asking. The point here is that she came to see my partner and me having already been started elsewhere on what many consider the last best hope—a "biologic." She had been using adalimumab (Humira®) for the prior six months. It may have cooled her a bit, but it will never address the underlying problem. It was simply not working, really. She needed immediate unroofing to spare her from ineffective I&D at her college's emergency room, and to spare her from the mutilating plastic surgery (a partial vulvectomy) that was being planned. After gentle peripheral local anesthesia by a well-trained medical assistant (who can take the time needed for proper unhurried anesthesia), all her wounds were unroofed. Several threatening milia, comedones, and small cysts were also detected and unroofed. She had the areas dried up with ferric chloride and coated with petrolatum, and she and her mother got on a plane for the 1000-mile trip home, thence back to school in a distant state (Figures 1.29, 1.30, 1.31, 1.32, 1.33, and 1.34).

In contrast, a patient with labial involvement untreated with the anti-inflammatory biologic discharged copious amounts of purulent material (Figure 1.35). Gently sponging away the draining pus revealed classic IPGM that was then removed (Figures 1.36 and 1.37). Worthy of note is that an I&D procedure (discussed further in Section 1.3.6) would have produced pain relief and a satisfying amount of blameworthy pus, but would have done nothing to eliminate the IPGM.

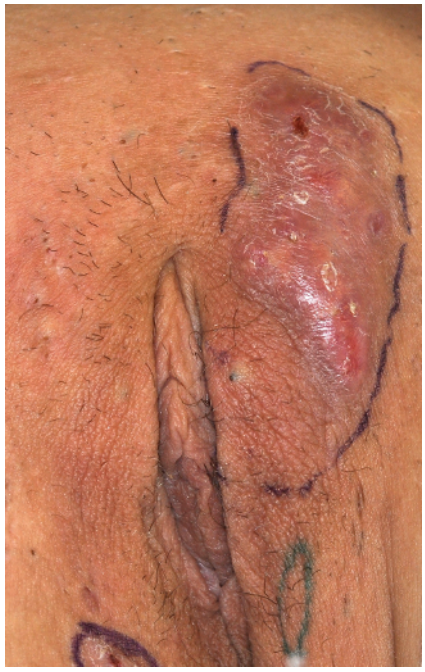


Figure 1.29 The lesion was uncomfortable, was not as painful as it had been, and was not as swollen, but it "just won't go away and keeps getting bigger."

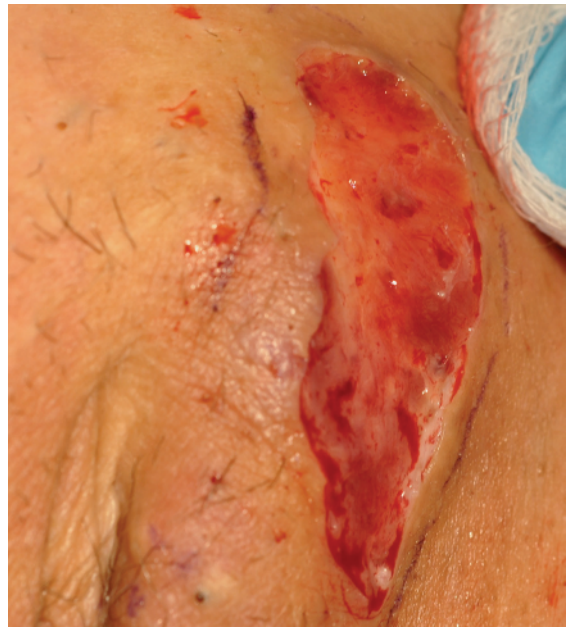


Figure 1.31 Looks pretty clean. Maybe just a little ferric chloride and petrolatum, and that's all that is needed?

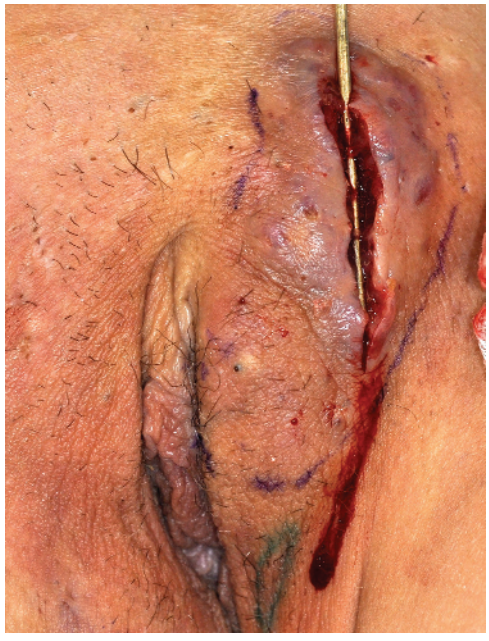


Figure 1.30 Not a drop of purulent material was released, a useful condition most likely attributable to the adalimumab.

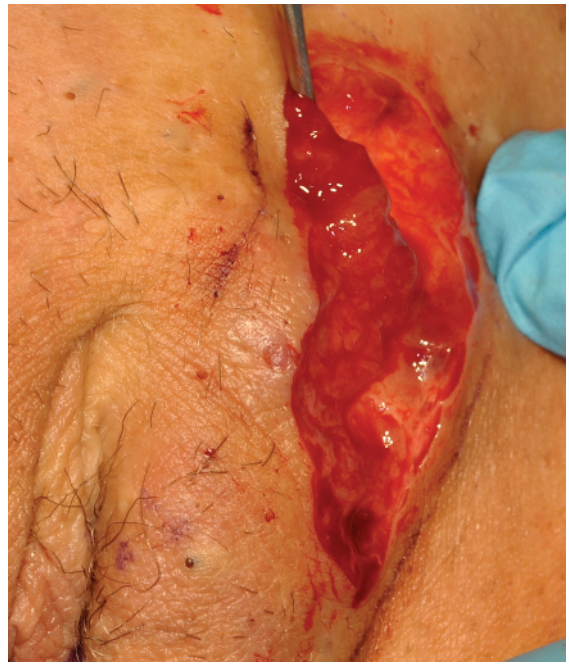


Figure 1.32 Looks like there is something else here besides pus or keratinous debris.

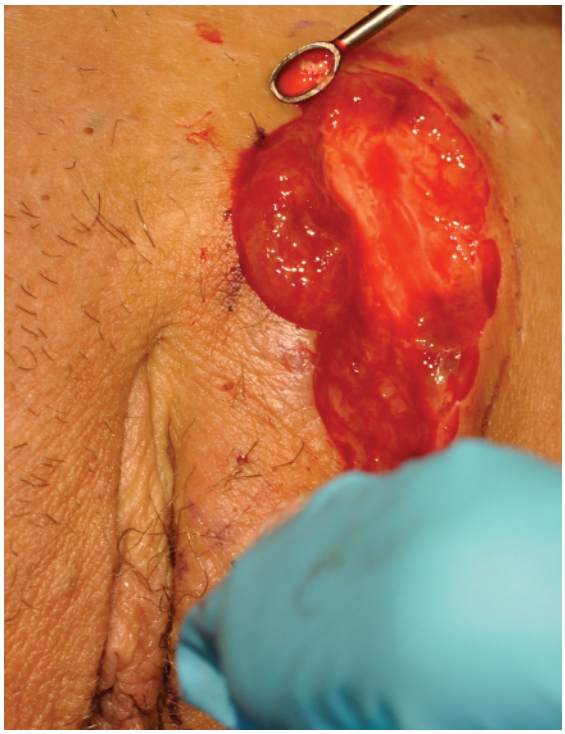


Figure 1.33 This is not keratin, it is not pus, it is not granulation tissue, and it is not fat. This is the invasive proliferative gelatinous mass (IPGM).

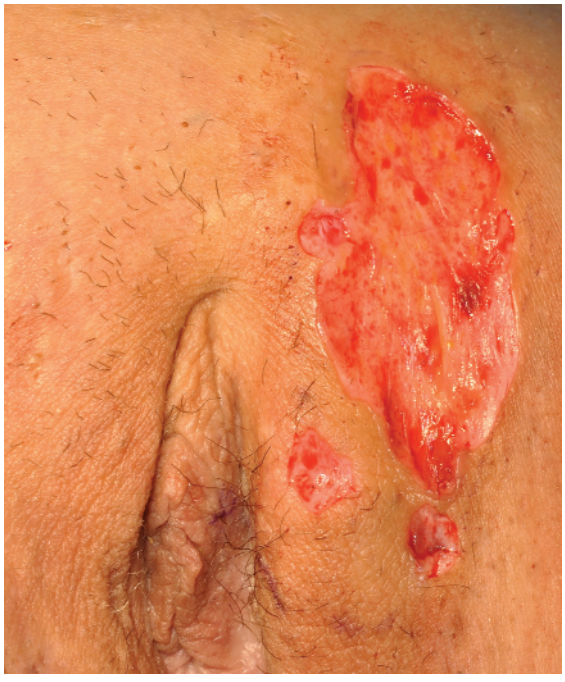


Figure 1.34 Here is the clean base of the lesion: uninfected dermis that will heal beautifully with nothing more than petrolatum.

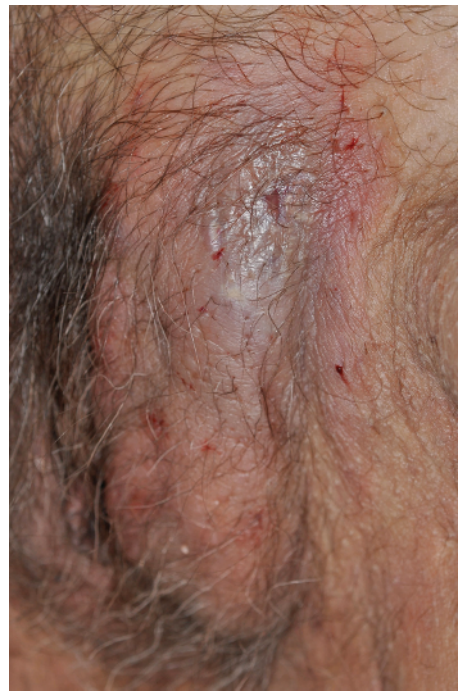


Figure 1.35 This very tender lesion was about 2 cm × 5 cm. It was a much more impressive red before the local anesthetic was placed.

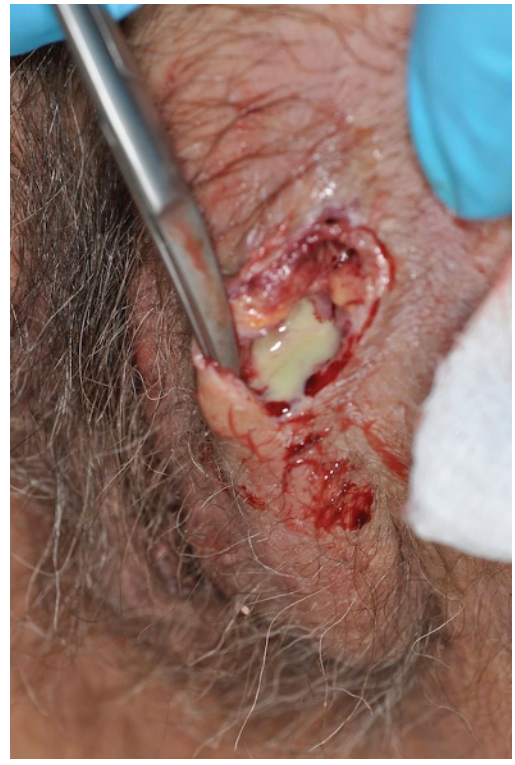


Figure 1.36 The purulent drainage is a reliable indicator of the degree of pain.

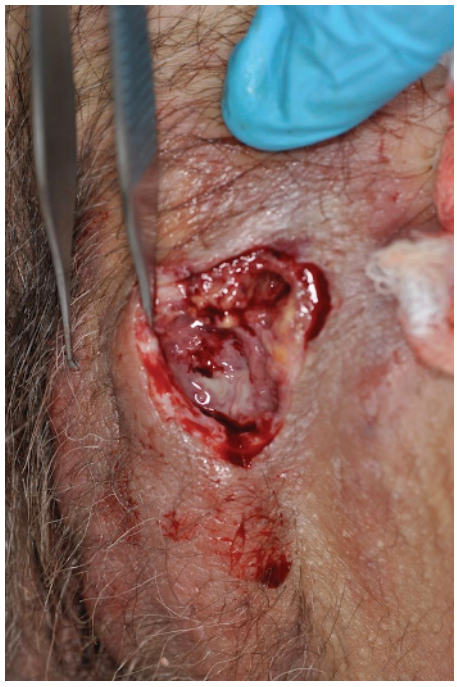


Figure 1.37 Under the purulent material, there is characteristic invasive proliferative gelatinous mass (IPGM).

1.3.6 So how do you get rid of all this material?

The first step is, of course, making the correct diagnosis. Sufferers from AI/HS will almost always have had experience with receiving the erroneous diagnosis of "boils" and having the I&D (incision and drainage) procedure done in their physician's office, a clinic, or the emergency room (ER). Hot, fluctuant, secondarily infected lesions are unbearably painful and the I&D gives almost instant relief, even if it is little more than a stab wound administered after a quick blast of ethyl chloride spray. Unfortunately, as succinctly put by Professor Jemec in the *New England Journal of Medicine*, "Lesions treated with incision and drainage routinely recur" [20]. The reason is simple. Failure to remove the IPGM perpetuates the problem.

Figure 1.38 illustrates a case in point, a patient who had two flared AI nodules on the underside of her left breast. She was unable to arrange to attend our office, so instead she visited a local ER where I&Ds were performed and she was placed on antibiotics. The relief was short-lived so she sought further help, and when she arrived I was able to obtain punch biopsies of both I&D sites. The

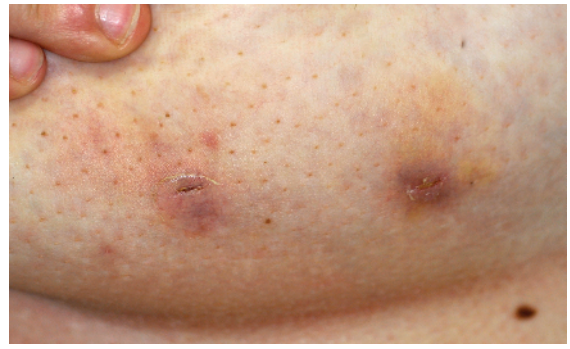


Figure 1.38 These were both incised and drained (I&D'd) about 5 days prior with simple stab wounds. Note the profusion of plugged pores in this inframammary area.

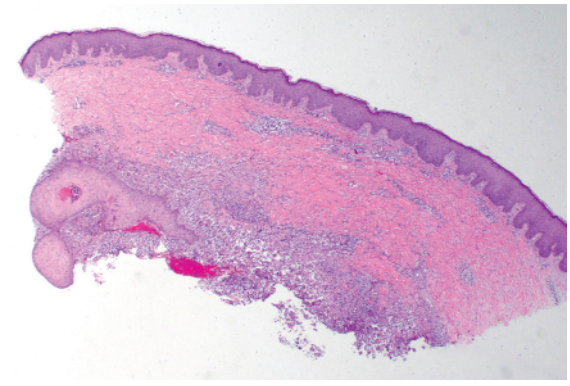


Figure 1.39 This is the top of the specimen removed using a punch biopsy, about a week after the patient had had an I&D in the emergency room. Note the residual mass of actively growing keratinocytes trying and failing to repair the ruptured FPSU. The inflammatory infiltrate that was producing the swelling and pain is obvious; indeed, beneath this there was significant abscess formation and foreign body reaction.

residual debris contains fragments of the destroyed follicle wall (Figure 1.39). This material not only is the stimulus that triggered her innate immune system's hot response but also is thought to be the source of the stem cells that would, if left behind, lead to development of the sinus tracts that are the hallmark of AI/HS.

So, how does one avoid such local recurrences? See Section 8.7.2.1, "Mini-unroofing."

1.3.7 What does the future offer?

A recent excellent review concluded with the words, "Future investigations should be dual and more focused on the pathogenesis of HS at immunological and

bio-molecular level. The focus should be on molecular genetics, biophysical effects on the hair follicles in response to shearing forces, the role of microbiotic flora and aberrant immunological pathways" [21].

Current research aims to identify the prime factors that cause and allow the follicles to burst. The bacteria, their biofilms, and the immune response to these organisms are all secondary—they are epiphenomena. Shearing forces are doubtless triggers, but what is the biomolecular abnormality that differentiates the unfortunate individual, whose sheared follicular unit leads to AI/HS, from the rest of us in whom no such problem ever occurs despite identical trauma?

Recent research demonstrates a defect in the lower part of the follicular unit, at the sebofollicular junction [16]. Present speculation suggests that this defect may have to do with an error in metabolism of collagen or another component of support protein. It is likely hereditary and may perhaps be contributed to in part by low ascorbic acid levels, either on a dietary basis or as a result of smoking. This occurs in a follicular unit that is overexpanded as a result of dietary hormones and growth factors in dairy foods and high-glycemic-load diets, just as happens in acne inversa's little brother, acne vulgaris. The combination of dairy, our modern high-glycemic-load diet, a simple vitamin deficiency, nicotine, and a genetic weakness may eventually be shown to be the kindling and fuel for a lifetime of misery.

1.4 The psychology of acne

If one were to list the stresses of the teenage years, I suspect the top seven would be acne, drugs, family, friends, money, school, and sex. The numerical rating given each would vary from teen to teen but, for many, acne and its psychological impacts overshadow everything they do. Acne vulgaris is bad enough, but AI/HS in a young person can be truly devastating.

1.4.1 Acne as a stress

When I discuss the hormonal causes of acne with patients, I tell them that the hormones that make acne worse come from three sources. The first is their own internal hormones from their ovaries or testes. The second is from various factors in their diet. The third is a small group of hormones related to stress.

The original paper on stress and acne was based on a small study done on students [22], but it doesn't take many days of working with patients to realize the profound and tight interactions between stress and acne. If you practice in a college town, the cyclic impact of midterms and finals is undeniable.

I point out that one of the ways to reduce the impact of stress is to get the acne better as fast as possible so that patients will feel better about themselves. Gaining control as quickly as possible means they will not need to "stress out" about new acne lesions popping up at irregular, unpredictable, and downright "just not fair" times.

This gives me the opportunity to explain to them that acne caused by stress has been considered for years to be a response to hormones from our "stress glands," the two adrenal glands that sit on top of our kidneys. Most have heard of adrenalin, and they can easily associate that with adrenal glands. They need to know that the adrenalin (*epinephrine* is a synonym) reaction to stress is the "first responder," and the adrenal steroid hormones that trigger acne are much slower to respond. They also come from a totally different part of the gland.

Until recently, the accepted chain of events has been as follows. Stress triggers the release from the pituitary gland of a small polypeptide hormone called *adrenal corticotropic hormone* (ACTH). ACTH's job is to turn on the adrenal glands, increasing their production of several hormones. In addition to cortisol (which helps the body deal with stress), the adrenals also produce testosterone and other hormones like dehydroepiandrosterone sulfate (DHEAS) that can turn into testosterone right in the FPSU, causing more acne.

It has been thought and taught for years that stress-induced acne was an exaggerated response to these adrenal androgenic (and so acnegenic) hormones in predisposed individuals. This is termed "functional androgenic hyper-responsiveness to ACTH" [23]. It resembles an exaggeration of adrenarche, the "start-up" of the adrenal glands that is the real first sign of puberty, even before pubarche, which is the start-up of the ovaries and testes.

This slow pathway likely still contributes to the chronic steady hormone load that operates to help trigger acne, but there is a new player that seems to have a quicker and more direct effect. This faster pathway is stimulated by a chemical called corticotropin-releasing hormone (CRH) that is one step before ACTH. It is the first polypeptide hormone in the chain of command

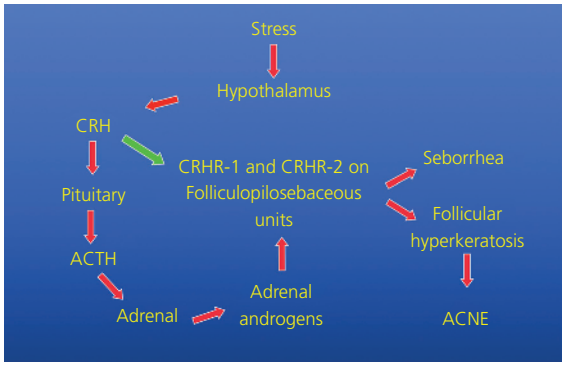


Figure 1.40 The red arrows illustrate the traditional link between stress, the corticotropin-releasing hormone (CRH) it stimulates, and acne. The green arrow illustrates what is now considered the "shortcut." Just to make life interesting, CRH receptors are also present on eccrine sweat glands (that may be linked to the sweaty palms and soles caused by stress), and the FPSU seems to be capable of making its own CRH in its own intracrine system.

from the brain. CRH is activated by stress and is released from deep in the brain, in the hypothalamus. The classical sequence of events was that CRH was viewed as the hormone that released the ACTH, and the ACTH would take the stimulation message to the adrenal glands and they would then multiply the androgenic and acnegenic effects.

We now have evidence that corticotropin-releasing hormone (CRH) may have a life of its own. Recent studies show that the sebocytes in the FPSU have a pair of CRH receptors (CRHR1 and CRHR2), and these appear to be responsive to CRH from the hypothalamus (Figure 1.40) [24, 25].

So, in short, it may be that acne causes stress, stress elevates CRH, CRH triggers ACTH, and ACTH raises levels of acnegenic adrenal steroid hormones that cause acne, but CRH also may directly impact the FPSU, also causing acne. And that, of course, causes more stress, and around we go again.

To break the cycle, we cannot shut down the hypothalamus, or the pituitary, or the adrenal glands, so we need to shut down the acne. The stress will cool as the acne fades, at least as far as the stress is due to the patient's concern about his or her acne. The whole system will slowly but surely decelerate, like a car when you take your foot off the accelerator. This slowing takes months in acne vulgaris and years in AI/HS, but the results are worth the wait.

1.4.2 Acne and self-image

The physical consequences of acne are painful, unsightly, and even messy. The scars are too often permanent. The socioeconomic consequences include interpersonal difficulties, social isolation, altered job prospects, and sometimes chronic unemployment. Then there is the added expense of medications and medical care that leads to a decrease in disposable income. That limits some of life's pleasures.

The psychological consequences include loss of self-esteem, personality change, depression, anxiety, the self-destructive use of alcohol and drugs, and the aspect that concerns us most, the risk of suicide (curiously termed *suicidality*). If all acne patients could gather their strengths around them and turn their energies to overcoming this disorder, they could put the whole thing behind them.

1.4.3 Isotretinoin therapy and the psyche

If you have done any reading about the care of acne, you will have run into the question of isotretinoin and the risk of depression. There is a vast "literature" on the Internet, and a discussion follows in Section 8.4.2.2. But before wading into that very muddy water, it would be fair and wise to provide some scientific balance. Good news seems to travel so much more slowly than bad news, so this time I am going to put the good news up front.

Of recent special and particular interest is the news that isotretinoin, contrary to its Internet profile, seems to directly improve mood. Two fairly recent studies looked at this. The first looked at the psychological profile of patients treated with various topical preparations compared to oral isotretinoin therapy. At the end of the second month, quality of life remained more impaired in the topical treatment group compared to the isotretinoin group. At the end of the fourth month, quality of life and all psychological test scores had improved more in the isotretinoin group [26].

The second paper studied changes in psychiatric parameters and their relationships to oral isotretinoin in acne patients. Two psychiatrists employed four psychiatric assessment tools to evaluate 38 acne patients [27]. The patients were examined before oral isotretinoin and at two and eight weeks after starting the drug, using the Leeds revised acne grading system. Not unexpectedly, the severity of depression (using the Assessment of the Psychological and Social Effects of Acne [APSEA]) and

the acne score improved after eight weeks of oral isotretinoin treatment. What was not expected was the finding that the severity of depression decreased after only two weeks of treatment.

Unexpected or not, this observation certainly parallels what we regularly see in patients starting isotretinoin. Those of us in clinical practice have long noted that oral isotretinoin therapy alleviates depressive symptoms. There really is no treatment that brings with it such hope, and delivers such results, as isotretinoin. This second study details improvements in depression directly related to acne-related life quality improvements rather than to improvement in acne lesion grade. These results suggest a direct positive effect on mood, independent of the improvement in mood due to the disappearance of the skin lesions. In my patients, it usually abolishes the negative impact upon mood caused by the Internet as well.

We have known for decades that isotretinoin is the only medication that actively miniaturizes sebaceous glands, reduces sebaceous gland output, and reverses retention hyperkeratosis. It now appears that isotretinoin has been shown to lower Beck's Depression Inventory (BDI) scores as well.

1.4.4 The isotretinoin–depression question

Teenagers are not an easy group to study. This is particularly true when looking at questions of depression and suicide. There have been, for many decades, numerous cases of suicide occurring in individuals with (and without) acne in whom there was no prior sign of distress obvious to friends and family. When this has occurred in someone taking isotretinoin, the drug has been blamed. This leads to the question that we hear whenever we consider prescribing this drug. "What about the risk of depression, doctor? It is all over the Internet." It's a tough and serious question, and it usually is a front for the real and unspoken question, "What about the risk of suicide, doctor?" There is only one safe answer: "If you believe there is a risk and you wish to avoid that risk, you must avoid the drug." Some dermatologists have decided to do exactly that and will not prescribe it. More on this in Section 8.4.3.2.

But let's get back to the population at risk of suicide. Given the subject, which is "touchy" at best and almost a taboo subject, there are barriers to discussing this problem. Interviews with this age group and collection of sufficient data to be statistically significant are challenging, indeed problematic.

Nevertheless, a baseline of sorts was set out in a study of 9567 New Zealand secondary school students aged 12–18 years [28]. The study centered on "self-reported" acne, depressive symptoms, anxiety, and suicide attempts. The results showed that "problem acne" was associated with increased risk of psychological problems. Note that this refers to acne that is considered a "problem" by the teen reporting in the study. The study showed elevated odds ratios of 2.04 for depressive symptoms, 2.30 for anxiety, and 1.83 for suicide attempts. Basically, the mere presence of problem acne approximately doubled the risks of each of these three conditions. The New Zealand experience may be somewhat more concerning than the North American and European situation, but the reasons for this are not known. It may simply be that the well-contained population of New Zealand is easier to study, and the data more centralized, giving more accurate estimates than are available in the scattered health care "nonsystem" in the United States. Importantly, even after controlling (adjusting the data) for depressive symptoms and anxiety, the odds ratio remained at 1.50 for suicide attempts associated with problem acne. In simple terms, that means that even when there appear to be no signs of depression (visible or admitted) and no signs of anxiety, the risk of suicide is about 50% higher if you have problem acne but are otherwise identical to someone of your age, sex, and so on. This suggests the possibility that a significant number of suicides occur among a small subgroup of patients who concealed their true depressive and anxious feelings. This underlines the authors' conclusions: "Young people presenting with acne are at increased risk of depression, anxiety and suicide attempts. Attention should be paid to their mental health, and the importance of asking directly regarding suicide is emphasized" [28].

The bottom line? Suicide sometimes occurs in teens (and others) who hide their suicidal tendencies, whether they are taking isotretinoin or not. Their final act is a shock to all who thought they knew them well, including parents, teachers, fellow students, coworkers, siblings, and significant others. Reports of these incidents are filled with statements of disbelief, usually to the effect that the victim was happy, well-adjusted, and well-liked, and showed great promise for the future.

As Ms. Ian has sung, "It isn't all it seems … at seventeen."

So dermatologists must not expect such information to be volunteered. We need to ask; we need to open the door. For those of you concerned about the possibility or risk of planting the seed of "suicidal thoughts" that might be acted upon, the psychiatrists have assured us that this is unlikely. Indeed, it is the unusual teenager who hasn't thought casually about suicide, or experienced it in friends, classmates, or relatives. It may have even been a subject for discussion among teenage friends. A recent US study found that "9 percent of male teenagers and 15 percent of female teenagers experienced some stretch of having persistent suicidal thoughts" [29]. Bottom line? If you are a patient reading this, please be honest with your dermatologist or indeed whoever is doing his or her best to help you. If you are a dermatologist, ask.

A second baseline has been set by Dreno *et al*., who found that rates of depression among isotretinoin users ranged from 1% to 11% across several studies, with similar rates compared to those taking oral antibiotic [30]. They concluded that "isolated clinical case reports indicate a possible clinical relationship between depressive symptoms and isotretinoin. In these conditions, it appears today that the link between suicides and severe depressions has not yet been clearly demonstrated" [30].

There are indeed numerous other small studies and "isolated clinical case reports" concerned with depression, suicidality, and a possible link to isotretinoin. Several purport to show a link between the use of isotretinoin for treatment of severe acne and self-injury, suicide, and negative thoughts. Evidence to the contrary is now provided by analyses of two large databases. The review by the Guptas of 9.6 million US patient visits "failed to demonstrate an association between isotretinoin use and suicide" and further suggests that "suicidal behavior with isotretinoin represents an uncommon, idiosyncratic phenomenon" [31].

While any life lost to suicide is a tragedy, the blame must not be laid unfairly on any innocent bystander, whether family, friend, colleague, teacher, classmate, prescriber, or isotretinoin itself.

To put this in perspective, and I appreciate that this may be thought to be a somewhat self-serving statement, I have not seen one single illness precipitated by the discontinuation of dairy products by my personal patients over the last 35 years. Nor has anyone committed suicide because I stopped their dairy, although I have heard on several occasions the teen hyperbole "I can't live without my milk."

1.4.5 Isotretinoin in perspective

Isotretinoin is one of the few "wonder drugs" in medicine. Having practiced before it became available, and having seen lives ruined by the inability to control rampant acne, my perspective is broad and deep [32–35]. This drug has changed the lives of hundreds of thousands of patients, and yet the positive impact is not much in evidence on the Internet. The reason is pretty simple—nobody likes to dwell on past problems once they are satisfactorily resolved. Isotretinoin success allows patients to put their acne behind them, usually permanently, and get on with their lives. They really don't want to even remember the problems. They destroy their old photos and ask me to get rid of the "before" photos I've taken for their records.

Enough time has now passed that I see parents previously treated with isotretinoin bringing in their children and specifically asking for isotretinoin. This is the reverse of the situation years ago when the occasional parent would ask, after their offspring was cleared, "Can you please do me now?" Nobody knows the value of isotretinoin better than those whose lives have been turned around.

The positive psychological impact of isotretinoin on hundreds of thousands of patients has been massive, and has been massively underdocumented.

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