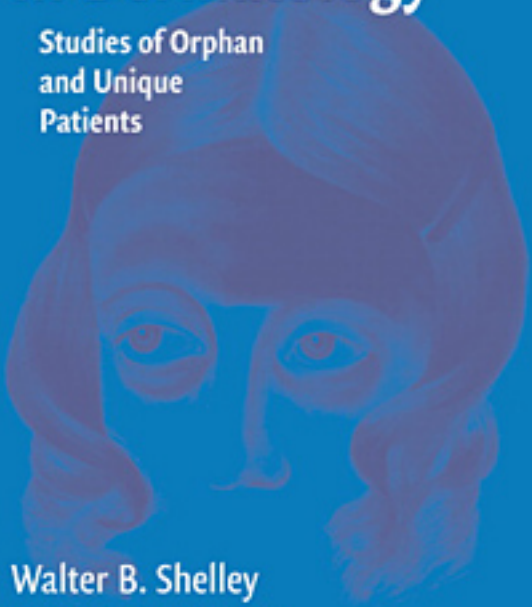
Consultations in Dermatology

Studies of Orphan and Unique Patients



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CONSULTATIONS IN DERMATOLOGY

This is a casebook on dermatologic differential diagnosis and clinical management, focusing on sixty-two challenging and vexing clinical cases that the Shelleys have encountered during more than fifty years of patient practice in dermatology. The management problems of these extremely perplexing cases go far beyond evidence-based medicine.

Each case is presented as a well-written vignette, told in a case-study tone. The authors first present the background of each case in a concise, thorough manner including all the important clinical details, such as tests and results. The authors then reveal the process involved in the diagnosis and the therapy involved.

Finally, they include a section called "Questions for the Doctor," which suggests relevant questions that the doctor should be pondering in each case.

For every unexplained skin change there is an undetected cause. Answers come to those who think, look, and act. Here is a book to assist the perplexed doctor and resident in their quest for understanding and cure. This is an excellent book for residents preparing for their boards.

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CONSULTATIONS IN DERMATOLOGY

STUDIES OF ORPHAN AND UNIQUE PATIENTS

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TO THE INQUISITIVE DOCTOR AND

THE PERPLEXED PATIENT

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PREFACE

Some time ago a patient came to us complaining of bright red palms. Her problem occurred only in the summer and faded each autumn. She had seen several physicians who could not explain her mysterious complaint. Her health was good, and tests for a liver or endocrine disorder were negative.

When we asked her what she thought was the cause of her red palms, the reply was, "I won't tell you because you will laugh at me, like the other doctors did." After convincing her we viewed her as our best detective, she finally said, "Watermelons."

Up until her visit to us she had been so ridiculed that she never put her theory to test. She felt that she must have an esoteric disease, which only a physician could fathom.

We simply had her stop eating watermelons and the rash promptly faded, even as it had in the last three autumns. A challenge was followed by a prompt reappearance of the redness.

Moral

Doctors – Believe what your patient tells you.
Patients – Trust your observations.

This is a case book of detective stories about patients who came to us with puzzling problems with their skin. Our practice has always specialized in helping the *orphan patient*. We mother over the patients with the rarest diseases. We welcome the patient who falls outside the family of ordinary patients with ordinary disease. We devote time and thought to

the patient whose problem cannot be solved in ordinary office visits. And from this practice, we bring you these stories of skin disease and its intriguing mysteries.

Too often these orphan patients find modern medicine indifferent to their complaint. Many are dismissed by disbelieving doctors. There are no grants or institutes dedicated to their care. Even though there are dozens of support groups for the study of defined rare diseases, as well as government support for the development of drugs to be used in treating these diseases, the orphan patient falls outside the circle of those who "care." Such a patient is a lonely example of his own disease, so rare that it is unrecognized and uncertified.

Many of the patients we describe in this book were told by their incredulous doctors and friends, "it's all in your mind." We hope that this detective book will show how sometimes "it's all in your skin."

We didn't include many of the mysteries we could solve easily with a good history or a simple skin biopsy. We didn't include the man with unexplained back pain due to shingles without blisters or the man with mysterious back pain in whom a skin biopsy showed microscopic smooth muscle tumors, which contracted causing terrible attacks of pain. Nor did we include the woman with thinning of her scalp hair, which was shown on a simple skin biopsy to be due to invisible sweat gland growths (syringomas) that shut down her hair growth. No, this book is about mysteries that took months or years to solve.

Some would say that we, as doctors, have used the approach of Sherlock Holmes in solving these medical mysteries. We would remind them, however, that it was Sherlock Holmes who was using the methods of medical deduction of his creator, Arthur Conan Doyle, a physician who learned them as a medical student at the University of Edinburgh. It was Doyle's professor, Joseph Bell, M.D., who was a genius at noting fine details, astonishing both patients and staff with his deductions and diagnoses. In appreciation, Doyle dedicated his *Adventures of Sherlock Holmes* to Joseph Bell, the original medical Sherlock Holmes. We have, accordingly, graced our first chapter with an epigram of Sherlock Holmes, recognizing its origin from the art of medical detection of more than a century ago.

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Finally, we bless John T. McCarthy (deceased), M.D., editor, and Sharon Mares Finch, publisher of *Cutis* for publishing our daily dermatologic diary every month from 1990 to 1995. They shared our concern

for the orphan patients whose rare, unusual problems remain outside the province of evidence-based medicine. This book is an extension of those diaries and welcomes all orphan patients and their doctors to experience-based medicine.

PROLOGUE

THE ORPHAN PATIENT

An orphan patient is one with a unique, inchoate, baffling, and often disabling disease not yet clearly discernible in the medical literature. Although technically this patient has an orphan disease – one defined as affecting fewer than 200,000 people in the United States – in reality he or she is an outlier, standing alone. With a cohort group closer to 20 than to 200,000, the orphan patient has no political constituency, no funding for research, and only serendipitous access to the rare physician with the time, energy, enthusiasm, knowledge, or research skill to "adopt" such a patient and solve his or her problem. Such a patient is a true foundling, often with a disease that knows no name and a physician who must turn away in sorrow and in ignorance . . .

Clinical medicine thrives on the study of the unique patient, as well as the study of DNA. Don't we in medicine need these orphans as much as they need us?

PRAYER OF THE ORPHAN PATIENT TO THE DOCTOR

Listen to me

- Don't be cynical, indifferent, or in a hurry.
- Ask me what makes my problem better or worse.
- Ask me what I think the cause is.
- Ask me to look for clues and teach me what they are.

Think about me

- Think of *my* problem when you read those books, journals, and atlases.
- Think of *my* problem when you attend meetings.
- Think of asking your colleagues about me.

Test me:

- Order specific tests to help you decide on my diagnosis and treatment.
- Could I have AIDS, cancer, or lupus?
- Do I need a biopsy? A challenge with a medication?
- Do I need hospital help?
- Do I need to see a consultant?

Don't give up on me:

- There is always one more treatment you can try. Just imagine I have a different disease and treat me for that.
- See me during an attack to get new ideas and new tests.
- Ask me lots of questions during every visit.

I won't give up on you, for I am an orphan.

INTRODUCTION

HOW TO BE A DERMATOLOGIC DETECTIVE

You have your whole day filled with removals and restorations, to say nothing of documentation and administration. Why become a Sherlock Holmes investigating the crimes committed in your patient's skin? Here's why:

Skin sleuthing is fun. Solving a patient's problem makes for a better day, perhaps not financially, but intellectually. It may take weeks, but the delight of satisfying your curiosity for the benefit of your patient is great. It is not enough to repair a wrecked car. You must know why there was a wreck.

Solving problems, explaining the inexplicable, is a higher order of achievement than making diagnoses. And, bear in mind, your patient is much less interested in the "what" of dermatology than the "why," but really wants to know both.

So, you want to be a Dermatologic Sherlock Holmes. It is not enough to don a deerstalker cap and smoke a curved pipe. You must acquire skills in these four areas:

1. THE HISTORY

Because many dermatologic diagnoses are simply labels for reaction patterns, it is up to you to look beyond the diagnosis and look for the cause. This is done best with a sharply focused history directed at probable or possible causes. All this calls for knowledge that comes from experience, from reading the literature, and above all, asking the patient what he or she feels is the cause.

We recall a patient at the University of Minnesota who presented with a swollen painful tongue. All of the attendants and residents felt a culture and biopsy would give them the answer. When it did not, they called on their chief, Henry Michelson. He simply asked the farmer, "What do you think caused this?" The reply: "I reckon it was a toothpick caught in my tongue," and so it was.

Knowledge and experiences can lead to sharply focused quick histories. We remember the CEO of a large corporation who had intractable rosacea. When asked how many cups of coffee he drank a day, the answer of twenty-five cups gave us a look behind the diagnosis and a cure.

History taking must not be passive. It should be probing. It should be detailed. It is not enough to ask, do you have a balanced diet? Witness our eighteen-year-old weightlifter patient who had developed severe cystic acne on his face and neck. A simple, yet focused, in-depth history disclosed the cause. He was drinking two gallons of milk a day. He was cured without retinoids or antibiotics by the simple elimination of milk.

History taking needs to be comprehensive, ranging from personal medical history to family history, occupation, and hobbies. Diabetes may explain the blister on the great toe. A family history may explain the blisters on the hand in porphyria. Chromium sensitivity may account for a hand eruption in those working with cement, whereas a golfer may be prone to poison ivy.

The history must center on medications. Drug sensitivity explains many a strange rash. Remember that a complete drug history is difficult to secure. Memory is feeble and often fails to recall the ordinary, routine events. Patients often have to be seen at the time of a flare to be successfully cross-examined. When you diagnose acute explosive skin eruptions, the best history is taken at the time of the flare up. We had one patient who had been hospitalized five times for attacks of erythema multiforme. She could give doctors no clue until we told her to come to our office within hours of her next attack. It was 9 A.M. Monday morning. The attack had come at 5 A.M. By going back over every inhalant, contactant, and ingestant throughout that night she finally said, "Oh, yes, I took an Ex-Lax at bedtime." It was that very medication that had eluded innumerable questionings by several dozen doctors and was the cause of each of her attacks, which was proven later by a blind challenge.

A history is best when it is layered, incremental, and repetitive. As the patient begins to know which of his or her observations you value

most, history taking becomes more profitable. And do not forget the clues provided by the patient's family and friends or other involved medical personnel. A vivid example involved an infant we had hospitalized because of unexplained blisters. All of our sophisticated laboratory studies were negative. The answer came from the floor nurse, who had noticed that the baby screamed every time her mother came to visit. Flinging open the door of the private room at the next episode of screams, she saw the mother applying a liquid to the baby's skin. It proved to be a strong acid.

Remain curious and your practice will always be interesting. We recall the professor at the University of California whose residents complained about the routine and boring nature of the patients on their ward. She said, "Take me to your most uninteresting patient." Once there, she elicited the following:

"Have you ever been in the hospital before?"

"Yes."

"Why?"

"Broken arm."

"How?"

"The boat shook me out of my bunk."

"What boat?"

"The Titanic." The residents learned their lesson when they saw the history they never took on the front page of the evening papers!

Taking a history is one of the most personal, friendly things you can do as a doctor. You bond with a fellow human being. You are a clinician privileged to glimpse another world. By having a deep interest in your patients' problems and treating them with warmth, you can provide them with a sense of hope, even when their problems remain elusive.

2. THE CONJECTURE

By knowing the patient's history and by viewing their lesions, you must now speculate as to the cause of the problem.

Could it be due to drugs?

Your history suddenly becomes more focused. What medicine does the patient take? Here it is necessary to use both direct and indirect questioning. They may deny all medicines, only to tell you on indirect questioning, "Yes, I take ibuprofen for headaches." They may need time

to rake away the leaves of forgetfulness, so that repetitive queries are often needed. You must ask about over-the-counter vitamins, laxatives, homeopathic concoctions, tonics, douches, eyedrops, and ointments. Also, be sure to check the contents of their over-the-counter remedies in the Physicians' Desk Reference for nonprescription drugs and dietary supplements. Chemicals come in many guises. All must be searched out, e.g., breath fresheners, lozenges, chewing gum, air fresheners, perfumes, disinfectants, moth repellants, and glues. We are exposed daily to hundreds of chemicals.

Litt's Drug Eruption Reference Manual (11th edition, 2005) is an invaluable aid in all of this detective work.

Could it be due to contactants?

Poison ivy is the most common troublemaker and do not let the patient dismiss it by saying, "I am not allergic to poison ivy, and I am never in it." Sensitivity may develop after years of handling it with impunity, and pets may carry the resin on their fur.

Again, the location of the lesions can help identify the causes of the problem, such as foot eczema in patients sensitive to leather.

The texts on contact dermatitis and occupational dermatoses will give you many clues. A visit to the workplace or the patient's home can yield unsuspected exposures not sensed by the patient. We recall a patient with a widespread contact dermatitis so severe as to require hospitalization twice. The case was solved only when we made a "house call" and were fascinated by her all aluminum kitchen. Her comment, "But I hate having to polish it," closed the case by revealing the criminal contactant never mentioned before.

Could it be due to foods?

Here the history must be provided by the informed patient. They must keep a detailed diary of everything entering their mouth. They must know the flare will come within two minutes to two days. Suspect foods in cases of urticaria, flushing, chronic hand eczema, and erythema annulare centrifugum.

Could it be due to an internal cause?

Some internal malignancies are heralded by skin disease. These include dermatomyositis, Bazex's syndrome, pemphigus, and necrolytic migratory erythema.

Other changes, such as Beau's lines in the fingernails, give clues of significant systemic illness over the past five months.

The most subtle internal cause for skin disease is focal infection. Watch for psoriasis initiated and maintained by chronic tonsillitis and streptococcal pharyngitis. Suspect focal infection as a cause of alopecia areata. Always look for the elusive periapical abscess, even if the patient has had good dental care. Think of focal infection in recalcitrant hand eruptions. It may clear only after cholecystectomy. Consider chronic cystitis as a cause for lichen planus. The search includes prostatitis and sinusitis.

3. THE INFORMED PATIENT

You have made your assessment and you now inform the patient as to possible causes. The well-informed patient is your most valuable ally in your search for the cause. Take unexplained pruritus as an example. Your patient must be made aware that your search is on for over-bathing, the most common cause of "winter itch" in the elderly. Next, that you suspect drugs including vitamins and homeopathic remedies, as well as chemicals in cough drops, chewing gum, douches, air fresheners, disinfectants, formaldehyde, and vitamin E creams. Next, comes suspicion of a low grade dermatitis from clothing, bath salts, hair sprays, or flowers. All of these are valuable leads for alerting the patient to his personal exposures. The best-informed patient gives the best history.

The patient then needs to have the appropriate medical studies. These may include blood studies for polycythemia and CT scans for Hodgkin's disease.

Any patient with pruritus or an unexplained dermatitis, also needs to have a KOH (potassium hydroxide) scraping for fungi and mineral oil scraping for the itch mite.

The patient must learn that what seems harmless, even though FDA approved, can turn on them and cause their malady. They must know that:

- eyedrops can cause an exfoliative dermatitis
- blood pressure medications can cause hair loss, along with many other medicines, including high doses of vitamin A
- cholesterol lowering drugs can induce dry skin
- a bouquet of Chrysanthemums, as well as their derivative insecticides, may cause intractable dermatitis

4. THE CONFIRMATION BY CHALLENGE

You have an incomparable advantage over your mentor, Sherlock Holmes. You can test your deductive reasoning by recreating the crime. You can reproduce the disease and thereby confirm or refute your conjecture. Dermatology has long provided this very satisfying venue for proving the cause.*

The challenge rests on your assessment of possible causes. In the case of dermatitis, the patch test is the sovereign challenge. Using standardized kits or improvised samples of the suspect allergen (proven innocuous on control individuals), one can reproduce a miniaturized version of the crime in two to four days under a closed patch. Subsequent exposure of the area to ultraviolet light (UVL) will permit confirmation of a photocontact dermatitis. Photodermatitis, per se, can be elicited by spot exposure to UVL sources.

The second challenge is with suspect drugs. Usually, confirmation comes with improvement and clearing of the eruption when the offending drug is discontinued. However, at times, this is a slow process due to persistence of the drug in the skin. Metallic drug antigens may remain for years as with silver and gold.

The simplest test is a closed patch containing the drug, but this is useful mainly in identifying the offender in the fixed drug eruption. For urticarial reactions, the scratch or prick test is available. Intradermal testing is also possible, but more hazardous. A direct challenge by the administration of suspect drugs orally or otherwise is the ultimate method for reproducing the disease, but must be used with great caution and the full consent of the patient.

Other indirect, yet conclusive confirmation of hypothetical causal primary or focal infections can be obtained through the use of antibacterial, antifungal, or antiviral therapy. A positive response to surgical excision of such foci of infection, e.g., tonsillectomy, cholecystectomy, or prostatectomy, is also striking proof of the validity of such hypotheses.

Many plausible or possible etiologic agents are found in the diet. After all, we are what we eat. Close attention to the history of suspect foods via

* Shelley WB. Experimental disease in the skin of man. *Acta Dermatol Venereol* 108: 1–38, 1983.

a food diary permits confirmation of an allergen by either elimination or challenge.

Recall that in all cases, for two to three weeks following a flare, the body may be totally refractory to an immune challenge, which leads easily to false negatives. Note also that a successful challenge may require two factors acting simultaneously. Thus, the patient with exercise urticaria and anaphylaxis requires a challenge with the food allergen at the time of the exercise. Similarly, allergy to fish may appear only in the cold weather of winter.

Imaginative challenges to airborne allergens and inhalants, including pollens and fragrances, may require breathing into a paper bag containing the suspected offender.

Verification of your suspects is most convincing with a positive challenge. But remember, simply eliminating all criminal suspects also ends the crime wave, to the delight of any long-suffering victim.

Repeated challenges may be necessary. We had one patient, a dentist, who had to experience a positive challenge with coffee three times before he would concede that his hand eruption was due to this beverage.

L'envoi

- Be a curious and inquisitive dermatologic sleuth.
- Be interested, because then your patient will become interesting.
- Be well informed, scanning texts, journals, and the Internet, and inform your patient as well.
- Be thinking of your patient's problem outside of office hours.
- Be imaginative, sympathetic, and optimistic.
- Be able to assimilate and coordinate random observations.
- Be like Sherlock Holmes and never give up.

1

THE CASE OF BLACK SWEAT

Improbable as it is, all other explanations are more improbable still.
– Sherlock Holmes

"Black sweat" was the complaint of a twenty-nine-year-old woman. For ten long years she had suffered from black droplets appearing all over her face whenever she became excited, tense, or overheated. She had seen numerous doctors who had no explanation and no cure. Indeed, many had doubted her story, because her skin appeared perfectly normal at the time of her office visit. The burst of black droplets would appear when she was dancing, and her partner would wipe them away, remarking, "you've got soot on your face."

Of far more concern than such embarrassment to this young woman was her mounting anxiety. Could the "black sweat" be a sign of black cancer? Was it a sign of the black plague? Yet, she seemed in perfect health. But neither she, nor anyone she knew, had knowledge of such an ominous secretion. Her doctors could provide no reassurance, because her problem was not in their textbooks of medicine. She was truly an "orphan patient."

When we first saw her, we were equally puzzled. We had only her history. Her skin was perfectly normal. There were no black spots. Could she be hallucinating? Could it be a form of the bloody sweat described as a stigmatization as in the case of Saint Therese Neumann? Could it be of hysterical origin? Or could it be a case of deception?

We had little to go on in the first visit. The phenomenon occurred only on her face; she described normal colorless sweat elsewhere. It was not due to pigment from the outside, because complete avoidance of all cosmetics for two years had not provided any help. Her earwax was of a normal yellow color. To study her problem, we needed to see it. Therefore, on the next visit, we placed her in a heat chamber. Within ten minutes, tiny black and brown droplets appeared on her cheeks. Before drying they could be wiped away easily, but if left undisturbed they dried rapidly, forming adherent shiny black flakes. The droplets appeared to come out of the pores of the oil glands of her face.

We now knew she had a rarity of rarities, colored sweat, termed "chromidrosis." Although textbooks were of no help, a search of the medical journals revealed it was first documented in 1709 by James Yonge of Plymouth, England. He recounted the terror of a sixteen-year-old girl whose face would turn black five or six times a day. The color could be wiped off, "smutting the cloth." He found the material to be unctuous, like grease and soot mixed, with no taste, and remained puzzled as to its nature. Although isolated examples later dotted the medical archives, many observers felt chromidrosis could best be explained on the basis of dissimulation and artifact. But in 1864, a French professor of Naval medicine in Brest, with the colorful name of Le Roy de Méricourt, proved by careful study of nine patients that colored sweat was real, and christened it "chromidrosis." He also distinguished the false or "pseudochromidrosis" in persons attempting to deceive by the external application of dyes. His charming little book on chromidrosis remains the solitary book on this problem.

Recently, a flurry of concern over "red sweat" in airline stewardesses proved that chromidrosis could also be accidental. In their case, it was due to a red dye coming off of life jackets used in safety demonstrations. And now we know that localized red sweat can be caused by bacteria. The cure is erythromycin.

But why was our patient's sweat black? The scattered accounts gave no explanation. To help, we needed to know more. Our first step was to take a small sample (biopsy) of the skin of her face. Under the microscope we found the answer – a special type of sweat gland filled with dark pigment. This was an apocrine sweat gland, which was normally found only in the armpits and genital area. This gland is responsible for body odor, although

the secretion itself has no odor until exposed to bacteria growing on the skin's surface. Deodorants, which are all antibacterial, help counteract the odor.

This apocrine sweat gland is a primitive gland from which a milky secretion empties into the oil gland pore. It was from these pores that we had seen her black sweat arise. Because we knew by history that tension and excitement caused our patient to "sweat black," it was no surprise that an injection of epinephrine into her skin was followed rapidly by the appearance of black droplets. Epinephrine was released by her own sympathetic nerve endings in times of stress, producing the black sweat. We found that the secretion was pre-formed, and that once the gland was emptied, it took time to refill. Squeezing the skin could empty the glands mechanically.

Once we knew our patient had colored apocrine sweat, we could relate her "display" to the colored apocrine sweat seen in animals. At the zoo you can see the big red droplets of apocrine sweat of the hippopotamus. Red chromidrosis has also been recorded in kangaroos. Antelope sweat is blue, whereas gazelles have true black sweat. Animal skin is rich in apocrine glands, but sparse in the eccrine sweat glands responsible for body cooling. A famous German anatomist, Schiefferdecker, in the 1920's proposed to grade racial superiority on the number of apocrine glands found in the skin: The greater the number of apocrine glands, the more primitive the man.

We wondered if the apocrine glands so common in the armpit could normally be secreting colored sweat that was washed away by the watery colorless eccrine sweat that soaks our shirts and dresses. Using injections of epinephrine to produce apocrine sweat without the eccrine component, we found that 11 of 100 patients had some colored droplets of sweat. Yellow, blue, and green were the most common colors, but one had black sweat. None were aware of this, because the amount was so small.

Finding the source of the black sweat was easier than discovering the nature of the color. Chemical tests on our patient's glands and the sweat proved it was not melanin, which is the pigment that causes us to tan. Nor was it iron. The pigment turned out to be a fatty compound, lipofuscin. The chemical and enzymatic basis for this derangement remains a mystery.

What could we do for this orphan patient who was in danger of closeting herself away from society? First, we could remove her fears and her tears. She did not have black cancer or any other disease. Second, we taught her that these black glands could be emptied before a social engagement. A hot bath allowed her to "sweat black" in privacy, and gave her a day of complete immunity.

Once again, we were taught to believe in the history a patient gives.

QUESTIONS FOR THE DOCTOR:

- Have you actually seen the colored sweat? Do you believe the patient's history?
- Did you check for a dye or colored powder in the patient's work and home environments as a possible cause?
- Could cosmetics or clothing be coloring the sweat?
- Does the patient frequently eat any fast foods that are the same color as the sweat?
- Have you done a skin biopsy looking for colored sweat in the apocrine glands?
- Have you treated the patient with erythromycin?

2

A CASE OF HIVES THAT WOULDN'T GO AWAY

A woman came to us with a three year history of hives. For over 1,000 days and nights she has seen and felt her skin itch, turn red, stretch and swell in lumps, bumps, and welts. All this would slowly recede within a day without a trace, only to be followed by new hives without rhyme or reason. Hers was not a rare disease. Indeed, several million people in our country suffer from this chronic urticaria. Hers was a common disease but, as it turned out, the cause was so rare it had never been previously described.

Chronic hives calls for courage and patience on the part of the victim as well as the doctor. No disease has a more daunting and diverse set of causes. There is no quick fix. The cause must be found and eliminated. Otherwise, there is only the search for relief with a variety of antihistamines. These, in turn, have their own side effects, and their own drug interactions, a few having turned fatal. Likewise, the new cutting edge therapies with intravenous immunoglobulin, the immunosuppressant, cyclosporine, or "washing" the blood with plasmapheresis, provide only temporary relief.

Chronic hives calls for the best in Sherlock Holmesian medical detection. Before searching for the criminal, it is wise to review the anatomy of the crime. Although our patient had "chronic" urticaria, every bump and lump was really "acute." Only the daily succession of acute attacks made it chronic urticaria. What is urticaria? Each hive is the result of a massive outflow of fluid from leaky small blood vessels. This trapped fluid remains in the tissue until lymphatic vessels slowly carry it away. And what makes

the capillaries leak? It is histamine released from specialized cells, the mast cells, which sit on the vessels. This cell is packed with granules of histamine and other chemicals that open the capillary flood gates to wash away noxious foreign material, such as allergens. These guardian mast cells contain 1% histamine in their granules. Little wonder that antihistamines taken orally and diluted in your body fluids to a concentration of a mere one thousandth of this is of such modest help.

Urticaria gets its formal name from the nettle plant, *Urtica* species, whose stinging hairs contain pure histamine, ready for direct injection into any skin that rubs against it. Histamine, coming either indirectly from mast cells or directly from the nettle plant, accounts for the itch and red flush of hives.

But, how is histamine released from mast cells? It is here that allergy is the criminal. The cell is coated with a protein (IgE) on a receptor for this same protein (FcΣ RI), designed to combine with a specific allergen. Once the allergen to which the patient is sensitized reaches this IgE-coated mast cell, their specific union fires off the release of histamine and multiple other compounds, which produce leaky vessels and thus hives. The conundrum is: why do these patients' white blood cells decide to make this "IgE fuse" for histamine release, ignited by a formerly friendly compound, such as egg or shrimp? Even an antihistamine itself can trigger the IgE fuse, although the dye in the pill is a more likely agent of sensitization.

From this background we see that any of countless compounds can be the criminal. There are some 450,000 synthetic patented chemicals now suspect: Even the aroma of coffee counts for over 130 distinct compounds. Where to turn? Although we cannot see a fingerprint, we know that the suspect has to be in the vicinity of our patient and it does not have to be something new. She could just as well have developed the IgE fuse for a new drug or inhalant, as well as an old food.

Now comes the exhaustive history. No tests just yet, but a probing of every aspect of her life and her hives. This history-taking must be carried out at every visit. The patient is our best observer and our best thinker, once she knows how the crime is committed. We encouraged her to think of every subtle clue. There was no daily rhythm or cyclic pattern. The absence of a premenstrual or ovulating flare ruled out hormonal allergy. It was easy for her to rule out physical causes – the hives were not induced by

heat, cold, or pressure, or even the rarest of causes, water itself (aquagenic urticaria). She knew it was not due to stress or "nerves", as did we. There were none of the telltale red and white halos around the hives, which are seen with the cholinergic and adrenergic urticaria associated with nerve stimuli. She knew her problem was not due to foods, because she had been on a strict total elimination diet for two weeks without help. Nor was it due to a drug allergy, because her only medication was insulin and this, too, had been stopped with no help for her daily hives. The individual hives always faded in less than twenty-four hours, ruling out hives due to an inflammatory vasculitis, as in lupus. Nor had biopsy studies shown any specific disease. All of her comprehensive medical studies, including a chest x-ray, were perfectly normal.

Our patient's hives had remained an enigma to her previous doctors for three long years. They knew that no cause can be found in most cases of chronic urticaria. But we knew that no cause would ever be found if the search was called off. Although our patients may give up, we never do. And this patient stayed the course of intensive investigation.

We had previously seen hives of nine years duration due to occult dental infection, and always search for this. The clue came in one woman when we realized she was not allergic to any particular food, but that all chewing seemed to trigger the hives. Chewing released bacteria into her blood stream from a hidden dental abscess, eventually found and treated, curing her hives. In another patient, we observed that her hives were associated with the absence of food. She had no hives when she ate every four hours. Presumably, she was sensitive to her own hormone, glucagon, released whenever her blood sugar dropped. But for the patient we were now analyzing, neither eating nor fasting had any effect on her hives.

We next moved to specific zones of therapy as a diagnostic tool. Although the antiyeast compound, ketoconazole, cures nearly 30% of our female patients of their chronic urticaria, it had no effect this time. A series of systemic antibiotics, given to hopefully eradicate occult infection, also didn't help. She still needed antihistamines daily and occasional courses of cortisone.

The search focused then on her occupation. She was a hairdresser and had worked for seven years in the same salon with never a day of hives or skin trouble. She had been regularly exposed to the permanent wave

solution, glyceryl monothioglycolate (GMTG), known to induce contact dermatitis in as many as 25% of cosmeticians, and able to penetrate right through regular rubber gloves. But she had never experienced dermatitis, only the hives.

The singular clue in this haystack of facts was that her hives had begun just four days after a plastic bottle of glyceryl monothioglycolate had exploded in her face as she attempted to open it. She sustained irritation, but after a few days her swollen inflamed eyes, skin, and mouth healed with no residua. She had continued to work giving permanents with GMTG, feeling it was safe because it had never been reported to cause hives.

She noted that when she was away from work for an extended time, her hives faded. But economic factors prevented her from totally quitting her job. Because hives due to occupation are virtually always due to something inhaled, she wondered about a sensitivity to fragrances in the shop, including perfumes worn by her customers. But the onset of hives so closely associated with the accidental spray of GMTG led us to wonder if inhaling this fume could have lit the IgE fuse for her mast cells. It seemed preposterous, because tens of thousands of hairdressers use this chemical everyday, and not a single one had apparently ever developed hives from it.

The denouement came when we and the patient had the courage to skin test her with GMTG. We used a ten thousandfold (1:10,000) dilution of the 80% stock compound she worked with. We recognized, as did she, that infinitesimally small amounts of an allergen, such as egg white, can trigger anaphylactic shock. We had emergency support standing by, but no need to use it. The scratch tests with GMTG were repeatedly positive, producing wide bands of hives. None of the ten volunteers showed any hives from the same skin test. We never dared expose her to the fumes in a breathing test. The scratch tests were enough to show the culprit to be GMTG, previously incriminated only in eczema cases, but now at last found guilty of inducing hives.

The patient is no longer a cosmetician, but she still has occasional bouts of urticaria related to other inhalants. We suspect that they represent cross-sensitivity to chemicals related to GMTG.

Clearly, this patient demonstrated that urticaria is the queen of diagnostic challenges.

QUESTIONS FOR THE DOCTOR:

- Did you ask the patient what she thinks causes the hives?
- Does contact with hot or cold objects trigger the hives?
- Do the hives come out at previous sites of pressure (pressure points) on the skin?
- Does exposure to sunlight or tanning beds trigger the hives?
- Does bathing or simple contact with water result in hives?
- Are the hives surrounded by white halos, indicating that nerves and stress are the cause?
- Could coffee, chocolate, nuts, eggs, or any food set off an attack within minutes to hours?
- Did you have the patient stop using toothpaste, chewing gum, lozenges, shampoos, and douches?
- Does the patient take any medicines, such as penicillin, cold medicines, or headache pills?
- Did you search for yeast infections and tinea pedis, cruris, and unguium?
- Does your patient get cold sores?
- Do her hives get worse premenstrually, indicating possible hormonal allergy?
- Does your patient get sore throats, cough, or toothaches, indicative of a possible focus of infection?
- Could your patient have gallstones or a gallbladder infection?
- What about exposure to inhalants, such as perfumes, cigarette smoke, or cosmetics?
- Does it bother the patient to endlessly take antihistamines?
- Is your patient mentally prepared to ceaselessly examine what is behind every attack?
- Have you checked her blood for eosinophils, serum IgE, immune complexes, and serum protein electrophoresis?
- Did you obtain a chest x-ray?
- Does your patient have chronic diarrhea, suggesting a need for stool culture and a search for ova and parasites?

3

THE PAINFUL BATH

"I can't take a bath without crying, the pain is so bad," was the strange complaint of an eighty-two-year-old woman. She told us she suffered with severe burning pain in her skin following every bath. It had been a problem for over six years. The pain began within minutes after she got out of the bath and lasted for nearly an hour. It was so severe that she limited her bathing to once a week. The pain never came on as long as she was in the tub, so she tended to prolong her bath time. It made no difference whether the bath water was hot or cold. She had further learned that adding bicarbonate or salt to the bath water gave no relief. Staying in the bath for an hour or so seemed to reduce the amount of postbath pain, but she was unable to reduce the pain by repeated bathing every hour. Antihistaminics had given no protection.

Her problem was unique and we had only a few leads. It was not something she had experienced as a child, but had come on late in life. No one else in her family had this problem. We could find no reference to it in a computer search of medical articles. Could it be feigned? Could it be due to stress, hypochondriasis, a neurosis, or even a psychosis? As we became acquainted with this lady over a period of months, none of these possibilities seemed reasonable.

Could it be a drug side effect or reaction? But no medicine was being taken. The pain was widespread, not like the painful acrodynia of the hands and feet of children exposed to mercury. There was no sign of inflammation or prior skin disease, thus eliminating the pain patients experience with either erythromelalgia or even shingles.

We could uncover no cause by physical and neurologic examination. Her normal blood studies ruled out the possible factors of iron deficiency anemia or the opposite, an excess number of red blood cells (polycythemia). Two biopsies of the skin showed no disease.

What could the water be doing to her skin in such an invisible way? The question nagged us for months. The breakthrough came by analyzing her blood before and after one of her painful baths.

We found that during the painful time postbath, her blood levels of norepinephrine were 60% above her normal prebath levels. Because norepinephrine is the sympathetic nerve messenger, her pain seemed to be of sympathetic nerve origin instead of the usual sensory nerves which react under circumstances such as touching a hot stove. Recently, the primitive autonomic or sympathetic nerves have been shown to trigger pain in altered states, such as causalgia or reflex sympathetic dystonia. Our patient's pain somehow involved these sympathetic nerves.

With this in mind, we prescribed clonidine, a medication that acts on the brain to block the release of norepinephrine. A single dose of clonidine taken an hour before bathing would prevent her terrible postbath pain.

She now bathes with comfort. A clonidine a day has taken the tears away. We have christened her mysterious malady, *aquadynia (water pain)*.

QUESTIONS FOR THE DOCTOR:

- Have you checked her CBC, looking for polycythemia?
- Have you prescribed clonidine or propranolol?
- Have you checked her serum iron?
- Does your patient need treatment for anemia or polycythemia?

4

A SHOWER OF HIVES

"Showers give me hives," said a fifteen-year-old girl. She startled us with her complaint. Could she really have an allergy to water? Careful questioning revealed it had all begun with the sudden appearance of hives thirty minutes after waterskiing last summer. The hives were small mosquito bite-like bumps which appeared over her trunk and upper arms. Each hive had a distinctive red zone around it. They all gave a fierce itch, until fading away in an hour or two, leaving no trace.

Since that time, every bath and shower has been followed within minutes by these same small itchy hives. Indeed, swimming, sweating, or vigorous exercise did the same thing, although being under stress was not a trigger. She got relief by taking an antihistamine before bathing or showering.

We quickly proved the history was no hoax. Placing a wet towel on her upper back induced a fine crop of hives in that area within five minutes after it was removed.

But why? Was it something in the water? Was it the temperature? Distilled water, sea water, and salt solutions all elicited the same hives, whereas contact with alcohol or mineral oil produced no hives. In fact, coating the skin with oil prior to showering or adding bath oil to the bath reduced the severity of the attacks. Temperature played no role; hot as well as cold water produced the hives.

We could find no disease responsible, and extensive blood studies were negative. We had to conclude that she was really "allergic" to water, which was proven by the towel test. It was, of course, "allergy" to skin contact with water and not, as the fellow who ordered his drink of scotch

said, "Don't add any water. I'm allergic to water." We suspect that the water allowed some unidentified chemical to soak in from the surface of her skin, which then caused histamine release from mast cells around her hair follicles, inducing hives. Histamine induces leakage of fluid from the tiny capillaries in the skin. The role of histamine is further supported by the relief our patient got from antihistamines.

Yes, Virginia. There really is an "allergy" to water. And those who suffer from it should not also have to suffer the disbelief and ridicule of their family and friends. This condition can be found in the medical literature under the name we gave it, *aquagenic urticaria*.

QUESTIONS FOR THE DOCTOR:

- Does adding sodium bicarbonate to the bath water help?
- Does coating the skin with oil prior to showering help?
- Have you tried "hardening" the skin by immersing the patient in a bath every hour until no more hives appear?
- Have you prescribed different antihistamines to be taken 45 minutes prior to each bath?
- Have you checked your patient for possible HIV and hepatitis B infection?
- Have you given your patient a trial of the anabolic steroid, stanozolol?
- Have you tried PUVA therapy?

5

A PREMENSTRUAL RASH

"My complexion is awful" was the complaint of a thirty-four-year-old woman. She had been referred to us for treatment of a facial rash, which had resisted the therapies of a half dozen doctors over the past thirteen years. Several biopsies had been done with the principal finding being intense inflammatory changes around the blood vessels.

Upon examining her, we saw redness, acne-like pimples, some small blisters, and yellow crusts on her face. Her problem had defied not only therapy, but also classification. It wasn't exactly rosacea or acne. We were puzzled, but intensive questioning opened a door of understanding. We asked, "Does it get worse before your menstrual period?" Her answer was, "I have no idea – it's worse all the time." But several visits later she came in saying, "You know, it really *does* get worse before my period! I had never noticed that and you are the first doctor to ask me." We now suspected she was allergic to her own ovarian hormone, progesterone.

Years before we had demonstrated that women could become sensitive to their own progesterone. This hormone can induce a variety of skin changes, including itching, hives, and even water blisters. The clue to progesterone sensitivity is the observation that the problem is always worse just before the period – the time when the highest blood levels of progesterone are found. Once the menses are over, progesterone levels drop and the skin reaction abates. It is possible to prove the diagnosis of progesterone sensitivity with a skin test using progesterone.

But, our diagnosis proved to be wrong. A skin test with progesterone was totally negative. We were still controlling her eruption with

antihistamines and injections of cortisone, but the cause of all her facial blemishes was totally mysterious. We needed to know more.

Because the severity of her problem showed a regular monthly cycle, we asked ourselves, "Might she be allergic to the other major ovarian hormone, estrogen?" A skin test was then done with estrone. Not only was it strongly positive on the arm, but within five hours her face flared and by twelve hours new little blisters and papules appeared on her face. It was evident that she was allergic to estrone, because skin tests with this material produced no reaction in ten normal volunteer women. She had a truly specific "autoimmunity" to estrone, because fourteen other related hormones were later found to give negative skin tests.

Autoimmunity, that is, the patient's bizarre reaction to hormones or chemicals in her own body, is as inexplicable as the reaction to poison ivy. It is much more rare, yet it may develop to the thyroid hormone, for example. Even cortisone, the sovereign anti-inflammatory hormone of everyone's adrenal gland, may be turned upon by the body. For years this phenomenon had eluded clinicians who could not imagine that for some people cortisone salves made the skin worse rather than better.

With the demonstration that our patient was allergic to her own estrogen, we were able to give her specific help with estrogen receptor blockade. This was achieved with tamoxifen. Taken daily for the ten days before the onset of menses, tamoxifen gave her back her beautiful complexion of fourteen years ago. And, we could assure her that the menopause would bring her a cure.

We have subsequently seen that the spectrum of skin problems due to estrogen sensitivity is as broad as that of autoimmune progesterone dermatitis. It ranges from hand eruptions through blisters to generalized urticaria, as well as the acneiform eruption our patient had. Birth control pills, as well as oral estrogens given postmenopausally, can also bring on the condition.

All of this taught us to search for a history of "worse before menses" in any woman suffering from a strange dermatitis. Such a search involves teaching the patient exactly what to look for.

QUESTIONS FOR THE DOCTOR:

- Has your patient kept a calendar of skin lesion severity, which clearly shows midcycle or premenstrual exacerbation?
- Is your patient using any medicines containing female hormones (oral contraceptives, estrogen patches, and/or vaginal creams)?
- Have you done intradermal skin tests for estrogen and progesterone?
- Have your done challenges with oral estrogen, estrogen patches, and intramuscular progesterone?
- Does your patient ingest large amounts of phytoestrogens in foods, such as sweet potatoes or soy?
- Have you given your patient tamoxifen to block her estrogen receptors?
- Have you checked her serum estrogen level?
- Have you treated her two weeks premenstrually with antihistamines, such as clemastine fumarate or chlorpheniramine maleate?
- Have you tried other therapeutic options, including corticosteroids, danazol, and progesterone?
- Should your patient have an oophorectomy?
- Does your patient take supplements containing phytoestrogens, such as black cohosh or isoflavones?
- Have you tried a progestin-only pill?

6

UNCOMBABLE HAIR

"Funny hair" was the only diagnosis that had been made on a two-year-old boy. His mother said she had never been able to comb it. Indeed, the little lad's straw-colored hair stood straight out from his scalp and was totally noncompliant with the wishes of any comb. It was right out of the old German fairy-tale featuring "Struwel Peter." Here was a boy whose hair was a mess (Strüwel), never once combed, looking as if electrostatic forces were in complete control. Indeed they were.

But why? Not only was the hair noncombable, but it came out in clumps on gentle pulling. It grew very slowly and was the same length as it was six months ago despite never having been cut. The hairs were fragile and thin, and broke when they were twisted. Reflected light gave the hairs a spangled appearance. The eyelashes, eyebrows, fingernails, toenails, and teeth were all normal. His parents and brother, as well as other relatives, had normal hair. He had always been in good health, except for two attacks of ear infection (otitis media).

Under the microscope the hairs appeared to be normal, showing no nodes, knots, rings, twists, or fractures. Ultraviolet light examination revealed no evidence of ringworm infection.

It was not the physical examination, nor the blood and urine studies, that made the diagnosis. It was the scanning electron microscope. Using this powerful system, which enlarged the surface of his hairs a thousand-fold, we saw that nearly all of his hairs had long canal-like depressions along the shaft. Even more striking, the hairs were triangular instead of round or oval in a cross-section. This was the diagnostic "hair print" of the uncombable hair syndrome. Dermatologists have been accused of hiding

behind Greek and Latin diagnostic hedges, but here is one diagnosis that speaks with obvious authenticity and clarity.

Further magnification, using the transmission electron microscope, showed that his hair had a normal whorled fingerprint patterning on the inside. X-ray microanalysis showed a normal sulfur content. The unique trihedron shape of the hairs presumably accounts for failure of the hair to lie flat after combing, because fiber thickness, tensile strength, and elasticity have been shown by others to be in the normal range. Hair follows the rules of wire mechanics, which teaches that the bending rigidity of a wire is the product of the modulus of elasticity and the moment of inertia. The triangular hair is more rigid, because the moment of inertia for a triangular hair is considerably greater than for a round hair. The modulus of elasticity relates to the chemistry of the hair, and remains indeterminate.

Our young patient's problem was clearly congenital in origin. We were able to exclude several other genetic or inborn hair defects sometimes present in children with "funny hair," including monilethrix (beaded hairs) and pili torti (twisted hairs). With urinary chromatograms, we were also able to exclude inherited abnormalities of the amino acid building blocks needed for hair proteins. Copper deficiency was also ruled out.

But what needed to be done for this modern day Peter Strüwel? Although there are over fifty cases of uncombable hair syndrome published, treatments have never been successful. We elected to try the vitamin, biotin, because it has a remarkable effect in promoting hair growth in infants. In our patient, oral biotin in a dose of 300 micrograms three times a day was followed by measurable hair growth in three weeks. After four months of treatment, the hair fragility and abnormal hair loss were no longer a problem, and the strength of the hair roots returned to normal. The hair continued to grow 1.5 inches a month and was more pliable and able to be combed for the first time. Follow-up scanning electron microscopic pictures, however, still showed the trihedron-shaped hair. We could conclude that the hair had become combable as a result of chemical, not structural, change.

The biotin provided this child with a rapid return to tonsorial elegance. Otherwise, he would have had messed up hair until he was a teenager, the usual time of spontaneous improvement in other examples of this rare problem. For orphan patients with diseases that have no approved therapies, our best rule of therapy remains: If you can imagine it might help, it just might!

QUESTIONS FOR THE DOCTOR:

- Does your patient eat raw eggs, which could prevent absorption of biotin?
- Have you tried your patient on large doses of over-the-counter biotin?
- Have you examined your patient's hairs under the microscope, looking for twisting, banding, and fractures?
- Did you confirm the diagnosis using the scanning electron microscope to demonstrate pili trianguli et canaliculi?

7

THE MAN WHO COULDN'T SWEAT

"Why can't I sweat?" was a question of a twenty-three-year-old roofer. He knew he couldn't sweat. He had avoided the heat as a youngster, knowing that headaches, nausea, and shortness of breath always came with hot weather. He became lightheaded and feverish in the hot sun. His parents had told him it was a family trait, with his grandfather and aunt having the same problems.

He had long complained of tender painful fingers and toes, as well as strange red dots around his "belly button." The pain in his fingers became much worse when he exercised or became overheated. And the red dots were becoming more numerous. Now they were also on his thighs and scrotum.

As a child he had been able to avoid conditions of high temperature. But now, working in the heat was unavoidable. An hour's work triggered a fever of over 100°F. At work he kept a sponge and a 2-gallon jug of water at his side. He had absolutely no sweat for the evaporative cooling we all enjoy. He had never been seen by a dermatologist, but now, after twice collapsing and becoming unconscious at work, he came to see us about his lack of sweating.

The only thing we saw were numerous pinhead-size reddish purple spots, looking like raised tuffs of blood vessels in the periumbilical, pelvic, genital, and thigh areas. The blood vessels of his eyeballs were also enlarged and tortuous. A general physical examination and routine blood studies were normal, but his urinalysis showed significant amounts of protein, blood, and casts. We confirmed his inability to sweat both by an exercise challenge and by an intradermal injection of acetylcholine, the neurotransmitter for sweating.

The human body is marvelously equipped to keep its temperature close to 98.6°F, despite cold or heat. In the cold, radiant heat loss is decreased by reduction in the flow of the warm blood into the skin. Shivering also sets in to raise heat production from the muscles. Conversely, in hot environments, evaporative cooling is achieved by the secretion of sweat by the eccrine sweat glands. There are over 2 million invisible sweat glands spaced over the entire 2 square meters of skin. On thermal command they secrete almost pure water to provide uniformly distributed evaporative cooling. All of the glands in aggregate would make a respectable organ the size of a golf ball, but such an organ would be hopelessly inefficient for cooling the entire skin. The sweat gland must continue to work unseen, except for its product. Indeed, a person could live a lifetime in air-conditioned quarters without ever knowing whether or not he had sweat glands, providing he remained free of febrile illness. A number of children are born without sweat glands, and no one notices until the child collapses at a July 4th parade. These children often suffer with unexplained low grade fevers from exercise. In the past, some were misdiagnosed as having tuberculosis and were sent to sanitariums.

But why was our patient so dry when everyone else at work was dripping with perspiration? A skin biopsy was necessary to tell us if he had been born without sweat glands. But our biopsy told us much more. Yes, he did have sweat glands, but the prominent overgrowth of blood vessels indicated he probably had Fabry's disease. This was confirmed with electron microscopy, showing special chemical deposits in the blood vessel walls, nerve sheaths, and sweat glands. With damaged nerves and glands, he could not sweat.

What is Fabry's disease? It took the name of one of the doctors who first described it, easier to say than its more proper name, angiokeratoma corporis diffusum. Fabry's disease is not simply a combination of anhidrosis (inability to sweat) and acrodynia (finger pain), but a progressive disease that insidiously kills its victims in the prime of life. It is a disease that humiliates diagnosticians, with the mean age of recognition being twenty-nine years. The diagnosis would probably not have been made had our patient been seen as a child, as the trivial complaints are easily shrugged off in any busy practice. Yet, early diagnosis is desirable, because this disease is inherited.

These patients lack a single vital enzyme, α-galactosidase, necessary to eliminate the complex organic fats of their cell membranes. These undigested glycosphingolipids accumulate slowly in ever enlarging deposits

within vessel walls, nerves, and sweat glands. This wax-like material, accumulating day by day for years, finally plays havoc with more than the sensory nerves and sweat glands. Kidney function fails, neurologic disorders develop, and heart attacks and strokes supervene. Detection is easy, but suspicion is hard. All of these patients can be diagnosed with a specific blood test for that crucial defective or missing enzyme. This is done on the white cells of the blood.

The genetic pathway is well marked in a sex-linked recessive pattern. A single gene locus on the X chromosome is responsible. Because women have a second X chromosome to correct this flaw, the "Fabry's gene" is recessive and does not produce any disease in the mothers who carry the affected gene. However, once the defective gene is passed to a son, the disease begins. Because the mother has two X chromosomes, there is always a 50:50 chance the son will be normal. Some families quietly pass the gene defect through mother, daughter, and granddaughter without any sons being affected. The Y chromosome, found only in men, is perfectly normal.

Genetic counseling is always indicated, because prenatal diagnosis can be made by amniocentesis. But at any time it is the finding of absent or low level galactosidase that makes the in vitro diagnosis of Fabry's disease.

Having the disease spells a reasonably normal childhood, a compromised life in one's twenties, and a tragic deterioration in the thirties. However, gene therapy offers great hope. Gene replacement therapy using the recombinant human alpha-galactosidase is now in clinical trials. It has the promise of averting the inexorable course of this metabolic disease.

Our patient's mother was healthy, although as a carrier of the disease she exhibited a low α-galactosidase enzyme level. As she grows older, her only sign may be a loss of visual acuity due to deposits of the wax in her corneas. The 50:50 role of the dice was not quite fair to our patient's younger brother. He, too, was found to have a total absence of α-galactosidase in his white blood cells, which probably explained his only skin finding, the abnormally dilated blood vessels on the back of his ears.

By the age of thirty-one our patient showed failure of his kidneys, as well as his sweat glands. Fortunately, his life has been lengthened by renal dialysis three times a week. His younger brother now has anhidrosis and acrodynia, but no kidney problems yet.

Finding the answer for this man who couldn't sweat was instructive, intellectually satisfying, and enlightening. But when the future is so bleak, is it not perhaps better to remain in the darkness of ignorance a little longer?

QUESTIONS FOR THE DOCTOR:

- Has your patient ever been able to sweat?
- Have you tried to make your patient sweat using exercise, heat, mental arithmetic, ingestion of spicy foods, or an intradermal injection of acetylcholine?
- Did you check your patient for sweating using a starch-iodine test? (Paint the area with iodine, pat it dry, press a piece of computer paper on the area for two minutes, look for black dots.)
- Have you checked for angiokeratomas on his abdomen, thighs, and scrotum?
- Did you do a skin biopsy searching for the presence of sweat glands?
- Did you examine the skin biopsy for deposition of PAS-positive granules, ceramide trihexoside in blood vessel walls, sweat glands, and nerve sheaths?
- Did electron microscopy confirm that the granules were myelin-like concentric lamellar structures characteristic of Fabry's disease?
- Did you order the blood test for the enzyme, α-galactosidase, in your patient and his family members?
- Did you check kidney function?
- Does your patient have acrodynia-like pain of fingers and toes?
- Did you suggest genetic counseling to your patient?
- Did you take a careful family history, looking for affected males and carrier females?
- Did you rule out other causes of generalized anhidrosis (diabetes, hypothyroidism, multiple myeloma, hypothalamic injury, vitamin A deficiency, multiple sclerosis, Addison's disease, Sjögren's syndrome, or anorexia nervosa)?
- Is your patient taking any medications, such as atropine or quinacrine, which interfere with sweating?
- Did you rule-out leprosy?
- Does your patient have widespread ichthyosis, atopic eczema, lichen planus, or psoriasis, which might interfere with sweating?
- Have you tried your patient on α-galactosidase enzyme replacement therapy?
- Did your patient ever have exfoliative dermatitis?
- Could your patient have poisoning from morphine, lead, arsenic, fluorine, or thallium?
- Did you try to induce sweating with a pilocarpine injection?
- Did you refer your patient to an ophthalmologist to search for specific corneal dystrophic changes (cornea verticillata) and tortuosity of the conjunctival and retinal vessels?

8

SCRATCH BLISTERS

"My old skin ain't what it used to be. It slides off whenever I bump or scratch it," was the complaint of an eighty-year-old man. He had the problem for several months, particularly on his forehead where we saw a few small and large tense blisters. One long linear band of redness on the left side of the forehead was the site of a long scratch mark. He also reported isolated blisters on his back, forearms, and lower legs. The blisters appeared overnight or could be produced by scratching a spot. They did not itch and the eroded spots took as long as two weeks to heal. Redness in the area lasted even longer.

The patient was in good health. He had never had skin disease and was not even sensitive to poison ivy. We could rule out diabetes and kidney or liver disease, all known causes of blistering in the skin. He took no medications, so that drug allergy could not be the cause. Sunlight damage was minimal. Nor was it of viral origin typically presenting as blisters with depressed (umbilicated) centers. It was not the acute painful blistering of shingles. The blisters associated with cancer (paraneoplastic bullous disease) were also not likely, usually being much more dramatic in their presentation.

We could have called it "fragile old skin," but it proved to be a polysyllabic tongue twister, epidermolysis bullosa acquisita. In this not-so-rare condition, the outer most skin layer, the epidermis, loses its attachment to the underlying skin or dermis. The epidermis, with the thickness of typing paper, is attached to the dermis by fibrils of protein acting much like Velcro. In this patient's skin, they were being destroyed by an immunologic reaction. Hence, a scratch tore the epidermal sheath loose and tissue

fluid filled the space, creating the blister. This, in turn, was easily rubbed off, leaving a tender raw spot.

The epidermis which covers our entire body varies in thickness and adherence. It is composed largely of columns of specialized cells, the keratinocytes. Here is a cell that in the course of its thirty-day life span transforms and sacrifices itself to form a dead keratin sheath for protection. Sometimes, as in the potentially fatal disease, pemphigus, blisters form because the keratinocytes lose their adherence to one another, resulting in tears within the epidermis. But in our patient, the whole epidermis was lifting off. There is no bleeding, because the epidermis has no blood vessels within it; the capillaries remain in the dermis just below. In addition to keratinocytes, the epidermis contains only (1) melanocytes, which form the pigment of tanning and color, and (2) Langerhans cells that form the immunity defense barrier.

Local treatment with antibiotics and cortisone salves gave little help. The blisters continued to appear frequently. We had a diagnosis, but no treatment. It continued to intrigue us that most of the blisters were on his forehead, a site of years of sun damage. We also wondered if a nearby infection might be the cause, although he denied sinusitis, sore throats, or earaches, and his dental care was exemplary.

Why did he have these "scratch blisters?" The denouement came on Christmas Day. He suddenly developed a toothache, treated with a five-day course of the oral antibiotic, azithromycin. The toothache promptly faded and, mirabile dictu, there were no new blisters. But within a week of stopping the antibiotic, the dental pain and blisters returned. It was all beginning to be understandable. He had a dental infection, which was seeding the nearby skin with bacterial antigen. The immune response to this was not only in the tooth, but also in the Velcro attachment area of his skin. Hence, the loose skin that could be scratched off.

We referred him back to his dentist, who discovered on x-ray that he had a dental abscess of his right upper molar (so close to the forehead). It obviously had been present for all the months of blistering. By now it had produced a large localized swelling of the overlying gum. He was sent to an endodontist, who sterilized the apical abscess and did root canal therapy.

Now, two months later, he returned very pleased that he no longer has any "scratch blisters." The moral: It wasn't his old skin, it was his old tooth. We have found that whether it be hives, blisters, or psoriasis, "Cherchez le dent."

QUESTIONS FOR THE DOCTOR:

- Did you take a complete history searching for hidden infection (e.g., sinusitis, prostatitis, or cholecystitis)?
- Did you seek dental consultation to find hidden dental infection?
- Could the patient have been exposed to poison ivy?
- Are you sure the patient doesn't have shingles?
- Did you check for diabetes?
- Did you take a complete drug history, (including prescriptions, over-the-counter medicines, vitamins, herbals, eyedrops, patches, powders, and toothpaste) and look for causes of a possible bullous drug eruption?

9

SKIN DEEP PHOTOGRAPHY

"What's new for blue skin?" asked an eighty-one-year-old man. He had had dark blue-black discoloration of his skin for the past forty-one years, and wondered if anything could be done. It all began after the injection of a sclerosant solution into his severe varicose veins. Examination revealed extensive bluish areas of the lower legs, with streaks following the pathway of veins. On the trunk, the skin was a slate gray color, whereas the sun-exposed areas were blue-black to black. His face was disfigured with the color being most prominent on the sun-favored areas of the cheeks, nose, and eyebrows. The depths of his wrinkles were less pigmented.

The darkening had come slowly. He knew the cause. It was the silver nitrate that had been injected into his leg veins over forty years ago, causing the well known argyria. Back then there was an ever expanding pool of these patients, most of whom had taken Argyrol®, one of the most popular remedies. This silver protein compound was taken by mouth for everything from stomach ulcers to arthritis. Only recently did we realize that Argyrol® cured peptic ulcers by killing the causative *Helicobacter* spirochetes in the stomach, similar to modern antibiotics. It was truly a "proto-antibiotic." This was the same Argyrol® whose soaring sales brought monies for purchase of modern art treasures, now displayed in the Barnes Foundation Art Museum just outside Philadelphia.

Today, argyria is a rarity, usually seen only in older patients who had been treated for syphilis with the silver coated magic bullet, Salvarsan®.

Unprotected workers in silver refineries are also silver-marked. Sometimes, argyria poses a mystery as to its source. In one patient, it came from chewing photographic film to suppress his desire for cigarettes.

In our patient, a skin biopsy confirmed his color was due to silver, present as fine granules in the upper dermis of the blackened skin. They sparkled under the indirect lighting of darkfield microscopy. These were not seen in the slate-colored skin of the trunk. There was no increase in melanin, the tanning pigment, in either area. Electron-probe x-ray microscopy of the refractile granules matched the exact atomic absorption pattern of silver. This elegant tool identifies metals in tissue, including iron, copper, silver, gold, titanium, lead, and mercury. It also permits identification of the iodine component of the cardiac drug, amiodarone, now the most common cause of the "black face." Scanning electron microscopy detects and records the distinctive emission pattern of photons from respective atoms.

The mystery of our patient was not what caused his blue-black skin, but why the color was so accentuated on sun-exposed areas. It is here that the sunlight takes center stage. The silver compound injected into his leg veins had clearly been carried by blood and lymph vessels to all corners of his skin. But then, through the years, it took ultraviolet rays of the sun to induce growth of silver crystals to blacken the skin.

His skin was thus acting like a photographic film: Light was the trigger, and time the developer. His skin contains collagen, a protein that serves as a matrix for binding the silver compound. It is the very analogue of photographic film, where the matrix is gelatin, a derivative of collagen. In both cases the matrix blackens when exposed to light. In photography, the thiosulfate developer causes crystals of silver to grow rapidly to a visible size, producing a photo image. In the skin, the same crystal size is seen after years of prolonged sun exposure.

We see that the black areas of this man's skin are actually a skin-deep photograph. Inadvertently, the treatment for his varicose veins had turned him into a camera.

QUESTIONS FOR THE DOCTOR:

- Did you do a skin biopsy searching for deposition of silver particles free in the dermis?
- Did you analyze the tissue for metallic elements using roentgen diffraction analysis?
- Did your patient ever take any silver-containing medicine, which might cause bluish discoloration of his skin (e.g., Argyrol® for sinusitis)?
- Did he ever work in a copper mine, gold mine, or coal mine?
- Has your patient ever taken any medicines which can cause hyperpigmentation, such as minocycline, chlorpromazine, or amiodarone?
- Does your patient take niacin, which can darken skin?

10

THE BUG THAT NEVER WAS

"My itch is terrible, but I know what causes it. My itch is caused by a bug." This sixty-three-year-old man had incessant widespread crawling and biting sensations in his skin for three years. He blamed tiny bugs that were not directly visible on the skin, but could be seen by him when he brushed them off into a wash basin.

It was a serious matter for which he had previously consulted three dermatologists, an infectious disease specialist, a pathologist, a microbiologist, a psychiatrist, an entomologist, and three parasitologists. No one had ever been able to identify any insect, ectoparasite, fungal element, or glass wool in his many many samples. Nonetheless, he spent most of each day cleaning, spraying, and vacuuming his home to eliminate his "pathogens." He had bought an industrial vacuum cleaner, special air filters, and cartons of disinfectant sprays . . . anything to kill the bugs. At night he was unable to sleep due to scratching. His life was truly miserable.

At each visit he came equipped with a basin of water, colored blue with a food dye. He averred that the bugs were grossly visible when he brushed them off into the basin if the overhead lights were turned off, illumination being provided by transverse lighting from his flashlight. Strangely, these bugs had no bodies that he could see, but were essentially jagged legs.

Repeated examinations with a 2.75 power lens of the patient's "parasites" floating in the water revealed only dead keratin flakes of his outer skin. Thirteen skin scrapings studied under light microscopy again showed no parasites. Scotch tape strippings of the skin surface, two superficial skin biopsies, and high power studies under the scanning electron microscope

were equally unrevealing. House dust samples brought in by him harbored only the harmless household dust mite, *Dermatophagoides farinae*.

He did have lifelong atopic eczema, as well as diabetes mellitus requiring insulin therapy for the past thirteen years. Both of these problems spell itching for many patients. However, treatment of his atopic dermatitis with systemic and topical cortisone, four different antibacterial agents, and medications against herpes and yeast gave him no relief. We also gave him treatment for intestinal parasites. Even the immune suppressant, methotrexate, had no effect. We also failed to help using a half dozen local preparations, including the insect repellent, DEET. "But Doc, you gotta kill the bugs to help me," he said. A trial elimination of insulin, as well as each of the three drugs he was taking for heart disease, equally had no effect, proving he did not have a drug allergy.

It was evident our patient had a psychosis, known as "delusions of parasitosis." This fixed delusional state dramatically responds to a little known orphan drug, pimocide. It was developed for the treatment of Tourette's syndrome, but has proven to give rapid dramatic help to patients who have "bugs" that never were. We gave it to this patient, but he returned in a week saying he couldn't take it. Possibly, the bugs did go away and he missed their company.

Buy why did this patient have his delusions? We think we know. They appeared suddenly at the time he underwent coronary bypass surgery three years ago. There is a growing awareness that coronary revascularization procedures may induce major neurologic symptoms. These result from focal damage to the brain caused by plugging of critical tiny vessels from circulating fragments of the damaged coronary arteries, microblood clots, or even air. Poor oxygenation of the brain during the operation may also be responsible. In one study, 1% of over 3,000 patients suffered postoperative psychoses, beginning within three days of surgery. The human brain is a marvelously enfolded sheet of neurons. If spread out flat it would cover half a tennis court. Small wonder it takes a hit at times.

Even more common are the delusions that arise in stroke patients. One woman we read about had a "fly with crooked wings" come live in her ear after her first stroke. She named it the "Grand Capricorn." After further successive strokes, 227 little capricorns were born to spend their lives in her ear and cheek. It is noteworthy that our current patient had two strokes three years ago, but the timing of the delusions favored the coronary surgery as their cause.

Delusional states are fascinating examples of how close we live to the unreal world. We like to visit the world of these patients, but not live there. One such patient believed she had a large cockroach living in her left ear. She came to us because he was forcing her into an undesirable diet. At every meal he came down along her mouth to eat. If he did not like her menu, he bit her. She was losing weight because of her strict compliance with the cockroach's dietary demands.

Unfortunately, we were never able to get a CT scan or PET scan of our patient's brain. Newer studies show that delusional psychoses may be caused by an infarct of the right side of a diffusely atrophied brain.

We never give up on a patient. But patients may give up on us. Our man did after two years. We miss his darkroom, blue water demonstrations of the bug that never was. We wish him well in his continuing search, which he hopes the National Institutes of Health will undertake. Who knows, maybe there is an itch bug. Or is that folie á deux?

QUESTIONS FOR THE DOCTOR:

- Have other people ever seen these bugs?
- Have you done skin scrapings for scabies?
- Have you microscopically examined the debris brought in by the patient, searching for ectoparasites?
- Have you done a skin biopsy of a lesion?
- Has your patient recently undergone heart surgery?
- Is your patient a cocaine user?
- Is your patient taking any medications that might be inducing paresthesias or sensations of formication (e.g., nitrofurantoin, nicotinic acid, amiodarone, amphetamine, or doxycycline)?
- Have you prescribed a trial of pimozide to "chase away the bugs" causing the delusion of parasitosis?
- Does your patient use an artificial sweetener containing cyclamate?
- Does your patient take an herbal supplement containing echinacea or St. John's wort?

11

BLUE SPOTS

"What are these blue spots?" A mother had brought in her three-year-old daughter. Her story was astonishing. Her daughter had diabetes and she had developed pinpoint blue spots on her thighs, buttocks, and arms, each at the site of certain insulin injections. The spots did not itch and were not tender, but had not faded over a period of months. The mother had also noticed blue-black spots on the top of the rubber stopper of each insulin bottle as it was used, including both regular and protamine insulin. Puzzled by the pigment on the rubber caps, they switched from silicone-treated needles to polymer-coated needles. Both types were standard disposable sterile 28-gauge hypodermic needles. They made no change in the insulin brand. Once this was done, neither their child nor the rubber stoppers got any more blue spots. But why? What caused the blue spots?

Examination revealed about twenty blue to blue-black punctate spots on each upper arm with a scattering of these same points of pigment on the thighs and buttocks. They looked like tattoo spots, and a skin biopsy of one showed a streak of fine black particles extending down into the skin. Obviously, they were along the path of a needle insertion. They did not reflect light as seen with talcum powder. A special stain showed they were not iron, and x-ray spectrometer studies proved they were not of metabolic origin.

Examination of the silicone-treated needles and syringes showed no pigment on flushing with either saline or insulin. However, several needle insertions into the rubber stopper produced black pigment deposits on both the upper and lower surfaces of the stopper. Cutting the stopper open showed a line of black pigment along the needle pathway. But most

remarkably, simple wiping of the needles with a Kim-Wipe® removed a fine black substance. It was completely insoluble in water or any organic solvent. Again, an x-ray spectroscopy of the black line on the Kim-Wipe® showed the black material was not metallic.

Obviously, the little girl had been tattooed by her insulin needles. But how?

The double coating of silicone was used by the first manufacturer as a lubricant to make an invasive needle technique seem noninvasive. It contained the mysterious black agent, which was rubbed off as the needle passed through the rubber stopper of the insulin bottles and was then deposited in the skin. The silicone itself could not be held responsible, because it is a clear colorless water insoluble polymer. Because the microprobe analysis showed no metals in the silicone, skin needle track, or on the Kim-Wipes®, attention was directed to the steel needle. Basically, steel is an alloy of iron and a small amount of carbon, which is rendered "stainless" by incorporation of chromium. The needle is heat treated and electropolished to remove surface debris and defects. We knew of a spectroscopic study of thirteen brands of currently used disposable hypodermic needles that showed a representative composition: iron 70%, chromium 21%, nickel 8%, and manganese 2% (with all the other metals less than 1%). Carbon was present in all needles, but not detectable by this technique.

We feel that carbon was the culprit. It is the oldest and best known tattoo pigment. We believe it leaked from the needle shaft into the silicone. Chemically, steel can be a surprisingly fragile aggregate. The steel in the needles may have been altered by the unique micro-bonding process used to prevent the silicone from all being removed by the initial needle insertion into the stopper. Although the automotive industry has a multimillion dollar instrument for detection of carbon, we did not have access to it for direct proof.

Our patient was the first to be described with these insulin needle tattoos, but others have no doubt puzzled over their blue dots, which would be most dramatic in thin young blonde skin, as in our patient. No doubt, also, the company has changed its manufacturing techniques to prevent further tattoos.

But finally, why are the dots blue when the pigment that slid off the needle was black? It relates to the phenomenon described by the British physicist, John Tyndall, over 100 years ago. He showed that when light

waves shine through a medium containing extremely small particles, they are scattered with only the short blue wavelengths being reflected back, whereas the longer wavelengths are absorbed. We see the same coloration in a blue mole, which is really a brown mole occurring deep in the skin rather than on the surface. The carbon deep in this child's skin reflected back only the blue waves and hence appeared blue. It was Tyndall who first showed what the bluebird and the sky had in common. To this we can add the blue tattoos of the silicone-treated insulin needle.

QUESTIONS FOR THE DOCTOR:

- What does your patient think is causing the blue spots?
- Have you done a skin biopsy?
- Have you examined a skin biopsy specimen under electron microscopy?
- Have you done roentgen diffraction analysis on the biopsied tissue to determine the pigment composition?
- Has your patient ever been near an explosion, which could have caused a tattoo of foreign material?

12

WHITE SPOTS

"Can you do anything about getting my color back?" asked a forty-three-year-old black man with depigmented skin of his hands, forearms, lips, and ears. His affected skin areas were ivory in color. The pigment loss had begun on his hands within months of being assigned to a new job as dielectric tester. Although he had worked for eighteen years at the same company, a spark plug factory, this was the first time he had worked with a solvent. Despite wearing synthetic rubber (Neoprene®) gloves, his hands were frequently wet with the solvent, tetrachloroethylene (perchloroethylene). Because the factory environment was hot, he frequently brushed away sweat from his face with the solvent-soaked gloves. He worked in this setting for three years until being transferred, and during this time the white skin areas enlarged. Particularly significant was the pigment loss on the ventral forearms, a site of contact with the solvent when he rested his arms. He denied any strange sensations or tightness in his fingers.

Once he had been removed from the solvent work, there had been some repigmentation of his fingers. There was no family history of vitiligo, the idiopathic heritable loss of color. Nor did he have any associated illness. He denied taking any medications. Detailed studies of his blood and urine showed them to be normal as were x-rays of his hands.

A biopsy of the affected skin showed an absence of melanin pigment in the epidermis, but otherwise nothing unusual. Closed patch tests to both the neoprene glove material, as well as the perchloroethylene (diluted to 25% in olive oil), were negative. No depigmentation ever developed at the patch test sites.

Loss of pigment, i.e., leukoderma, is not a rare occupational disease. It is seen most commonly in individuals who handle or use disinfectants, particularly the phenolic germicides. It can also occur as a result of wearing rubber gloves containing hydroquinone. This rubber additive produces an immunologic destruction of the melanocytes which manufacture the brown melanin, which colors our skin and protects us from sunlight. Although melanocytes make up only 5% of the epidermis, their spidery pseudopods enable them to pump melanin, the natural sunscreen, into adjacent cells that specialize in growing a thick but dense coating of keratin for the entire body.

Once the melanocytes are destroyed by chemical or physical means, pigment production stops and the color never returns. In the case of vitiligo the melanocyte is crippled by an immunologic reaction – a sort of autoimmune inflammation. At times it is amenable to steroid therapy, but in the case of permanent loss of pigment, the most successful treatment involves very superficial skin grafts taken from the patient's own areas of normal pigmentation and placed in the depigmented areas.

We have seen localized perioral pigment loss from rubber bands used in orthodontic care. We have seen it from superficial fungal infections, as in tinea versicolor, whose very name discloses the color change. But we have not seen it from solvents. Still, we feel that his three years of daily exposure to perchloroethylene was the cause of his white spots. It apparently was a toxic, not allergic, reaction, because no inflammation was present in the skin biopsy.

Regrettably, we could not reproduce the pigment loss on patch testing. Any agent suspected of producing leukoderma must be left in contact with the skin for two to four weeks to permit cumulative toxicity and allow shedding of the old pigmented epidermal cells. Sometimes it takes two to three months for the new epidermis to come out from the shadow of the old. The standard forty-eight-hour patch test, so useful in eczema detective work, is not useful in studying depigmentation. We used the standard two-day closed patch test, because we did not think his epidermis could stand weeks of challenge with the perchloroethylene.

The role of the neoprene gloves is also not above suspicion, because neoprene adhesives have induced leukoderma.

After all of our studies, we had to say we could not do anything about getting his color back. Long sleeves and gloves still remain his best treatment.

QUESTIONS FOR THE DOCTOR:

- Are the white spots symmetrical, which is typical of vitiligo?
- Has your patient ever worked with phenolic chemicals or disinfectant cleaning solutions?
- Does your patient work with hydroquinone in the leather or rubber industry?
- Has your patient had a previous skin disease, which could have caused post-inflammatory hypopigmentation?
- Has your patient ever worked while wearing rubber gloves?
- Where was the first white lesion, and is there a pattern to the development of later lesions?
- Did you check for the presence of focal infection underlying the initial white spot?
- Does the patient have any infected teeth?
- Have you checked for prostatitis, cystitis, cholecystitis and sinusitis, as well as other possible underlying infection?

13

SAME PLACE, NEXT TIME RASH

"My daughter has got it again. She had to be hospitalized last time and no one knows what it is. Please help." We didn't practice on Saturdays, but early this Saturday morning we met a seven-year-old girl for an emergency evaluation of a fiery red rash, which was symmetrical on her cheeks, armpits, groin, and buttocks. It had come out just four hours ago and her mother was frantic. This was the third time her daughter had been stricken, each time in the same exact areas.

We learned that the first attack had occurred two years ago following a cough and runny nose, and had necessitated three days of hospitalization. There was no fever. Treatment with aspirin and an antihistamine resulted in fading of the rash without any trace later that week. Extensive studies revealed no cause for the rash, so the noncommittal diagnosis of "toxic erythema" was made. The second attack came just ten months ago. Again, no cause could be found, but hospitalization and treatment with intramuscular cortisone was necessary.

We continued with the history. Her parents and a three-year-old brother had remained well on each occasion. Yet, on this Saturday morning the girl looked and felt sick. Her joints were tender and swollen. She had complained of malaise the previous night and had slept poorly. The only medication given had been a teaspoonful of Night Time Cold Formula®, which contained pain relievers, a cough suppressant, and a decongestant.

An examination revealed no middle ear infection or inflammation in the throat. A throat culture proved negative, and the blood and urine studies showed no remarkable findings. To avoid hospitalizing our patient,

we gave her a course of oral cortisone. Within a few days the redness and tenderness were gone. This was followed by marked scaling, much as one sees after a severe sunburn. After three weeks, the skin was entirely normal with no discoloration.

The fact that the rash had appeared in exactly the same places each time reminded us of the fixed drug eruption. In this condition, random islands of skin become inflamed whenever the person takes the drug to which they are allergic. But always the spots remain dark brown for months, even years afterwards, and the rash never is symmetrical. Still, the same site involvement suggested to us that our little girl might have an allergy to a drug. Unlike the usual allergic drug reaction, however, this was localized to just the areas we were seeing.

But what drug? The Night Time Cold Formula® was the logical suspect, because it had been taken just hours before the rash appeared. There is no blood test for such allergies. Because of the repeated frightening explosive onset of this extensive rash, we felt a tiny oral challenge dose was justifiable. Thus, months later we gave our girl one-fifth of a teaspoonful of the same cold medicine. Within six hours the same red eruption appeared in exactly the same sites as her three former attacks. Fortunately, it faded within two days without treatment. Then, using very small doses of each of the five ingredients of the cold formula, we challenged our patient again. We knew that drug allergies are usually dose-dependent – the larger the dose, the more severe a reaction. We thought the cause would be the yellow dye, tartrazine, a significant cause of hives. However, this was taken without incident. In retrospect, we realized that tartrazine is a common coloring for foods and drinks, such as Tang®. Had she been allergic to this she would most certainly have had frequent attacks of her rash, not just those three attacks in two years. Nor was she sensitive to either the cough suppressant or the pain reliever components. The real troublemaker proved to be the decongestant, *d*-pseudoephedrine. Within the magic six hours of taking a small dose of this pure drug, she had new large tender raised areas on her face, arms, feet, groin, and buttocks. Her hips and knee joints became so swollen and painful that walking was difficult. It seemed evident that when she took the whole formula, even in a much larger dose, the other drugs in the mix protected her somewhat from the ill effects of the pseudoephedrine. Again, a week after this last challenge, her skin and joints were fine.

Her mother was happy to know the exact cause of her daughter's "same place, next time rash." By reading every label and avoiding all medications with pseudoephedrine, our patient has never had another episode of rash in the subsequent two years. This attention is necessary, because there are fifty-five different nonprescription syrups, solutions, tablets, and capsules that contain pseudoephedrine. Her doctors must also be informed, because twenty-two prescription items contain it as well.

Here is a drug used by millions. Yet, in the lottery of "ill chance" it can turn on a patient and produce a scarlet fever-like rash or an erysipelas-like eruption, hives, blisters, and even black and blue spots. In this latter case the unfortunate parent who only gave their child a cold medicine will be accused of child abuse.

QUESTIONS FOR THE DOCTOR:

- Has the rash occurred in exactly the same location before?
- Was the patient sick when the lesions developed?
- Did the patient take a decongestant cold or cough remedy prior to developing the rash?
- Did you photograph or diagram the rash for future reference as to exact location?
- Does the patient have any known drug allergies?
- What drugs, vitamins or herbals did the patient take during the forty-eight hours prior to onset of the eruption?

14

THE BROWN SPOTS THAT WOULDN'T GO AWAY

"Why do I have these brown spots?" was the query of a thirty-seven-year-old woman. She didn't seem too hopeful of getting an answer. She had made innumerable visits to her family doctor and to emergency rooms over the past three years. No one knew why she had had that large brown area over her left hip all that time. And another big brown patch had appeared on her right knee just one year ago.

We asked, "but why the emergency room visits?" "Oh, every four to five months those brown spots get swollen, terribly red, and hurt bad." We then knew what it was – a fixed drug eruption. Every one of her alarming attacks over the past three years had to have been preceded by her taking the same troublemaker drug.

What drug was it? In most patients the search can be lengthy. There is no blood test. An oral challenge is necessary, although in a few patients simply applying the crushed pill or liquid medicine over the brown spot will set off a local red reaction, thus identifying the cause. In most instances the best detective work is done by the patient, once informed and on the outlook for what she or he has taken the day before the "fire" comes into the brown spots. The patient must realize that in some instances the red flare-up is slight, totally obscured by the residual brown pigment from past attacks. In these instances, the onset of tenderness of the brown spots will aid in detecting the cause.

In this patient a lengthy detailed history allowed us to suspect the specific cause of her brown spots. Her drug history included Nyquil®, Alka-Seltzer®, Naprosyn®, and Midrin®, all taken intermittently for the past few years. The Valium® she took regularly could be disregarded since

her attacks of emergency room urgency were intermittent. She also told us she had been taking short courses of Flagyl® for the past twenty years.

On further inquiry we learned that her last attack of redness and pain was two months ago, at which time she recalled having had vaginitis. She couldn't remember exactly, but, no doubt, she had taken Flagyl®. We gave her a single tablet of Flagyl® and the next morning her brown spots hurt. Later that morning they were red, swollen, and tender. She had her answer.

But she needed to know she must avoid not only Flagyl®, but also all the other brands containing the active ingredient, metronidazole. Read the labels, we insisted. We also advised her to avoid chemically related medicines, such as the antiyeast vaginal creams or suppositories containing miconazole, clotrimazole, and ketoconazole. No "azoles" at all!

It has been over a year now with no flare-ups and no hurried visits to emergency rooms. Her brown spots lie quietly as a souvenir of her unique islands of allergy. In every attack she dropped more of the brown tanning pigment of inflammation, melanin, into her skin as a sort of tattoo. It will not go away for a long time.

In the case of the fixed drug eruption, seeing the brown spots makes the diagnosis, but seeing them become inflamed helps you find the cause.

QUESTIONS FOR THE DOCTOR:

- Do the brown spots sometimes swell up and get red?
- Could the brown spots be due to a medicine, vitamin, or herbal taken only occasionally?
- Did you have the patient write down every oral medicine, vitamin, herbal, cream, powder, patch, eyedrops, inhalant, and douche used shortly before the brown spots began to redden?
- Did you rechallenge the patient with small amounts of the suspect medication to reproduce the fixed drug eruption?

15

THE CASE OF THE PAINFUL FINGERTIPS

"My fingertips hurt so much, I can't work," was the tearful complaint of this forty-year-old hairdresser. We looked at her fingertips and there was not a thing to be seen. They were absolutely normal; yet, touching them made her wince. Squeezing them made her scream. What was wrong? Was she malingering? Did she have a neurologic disease?

This was no ordinary case. She had seen a posse of physicians but no one had caught the criminal. The neurologists gave her a good bill of health and so did the psychiatrist. Her family physician had no special insight nor was the report of the peripheral vascular specialist helpful. Several dermatologists had provided no enlightenment.

Well, first things first. What was the exact history? The problem began last fall as marked sensitivity of the lateral side of the tip of the right fourth finger. Shortly thereafter, the medial tips of both thumbs were similarly affected. Eventually, all of the fingers became involved to a greater or lesser degree. Inflammatory changes were absent, but exquisite tenderness to touch continued and pressure on the fingertips always induced pain. There were no other sensory changes and her toes were not affected.

Her past history was noncontributory. Neither she nor anyone in her family had experienced neurologic or psychiatric problems. There was no history of skin disease or diabetes mellitus. She had worked for many years as a hairdresser, but knew of no new contactants at work or home.

From this feast of information and all of her laboratory studies we were able to rule out dozens of conditions which cause painful fingers, such as Raynaud's disease, mercury poisoning, and blood vessel glomus

tumors. We had seen foreign bodies, such as fragments of steel wool or cactus spines produce tenderness, but never on all ten fingers.

Our questioning then focused on the abrasive materials she might use in her work. It was then that we turned-up the real lead as to why her fingertips were so tender. Just three months before it started she had begun using a new "silica hair curler" instead of the regular rubber and plastic curlers. Our patient had been the fastest operator in the shop, handling as many as 450 curlers a day, six days a week, for those three months. In the course of use, these curlers lost their rough abrasive surface and had to be discarded.

Not only was our patient twirling these curlers and the hair, but she also did considerable wet work with alkaline hair sets and waving solution. It seemed likely that tiny invisible sharp fragments of the curler material could spin off and penetrate the macerated fingertips, with the embedded microparticles in the skin accounting for her unusual complaint. We felt she had a new occupational disease.

We had her bring us some of the curlers. They proved to have a surface rough with irregularly glued on grains of sand, which fragmented readily into microparticles. Spectroscopic examination confirmed that they were indeed silicon, with only trace amounts of other elements, such as iron and copper.

We returned to the patient's fingertips, examining them under high magnification (80 x) using a fine wire point for testing. We demonstrated that her tenderness was not diffuse, but very focal, precisely localized to specific points. Time and time again she identified the same punctate areas of pain on focal pressure. We marked these, then biopsied the skin. At each tender point, there was an irregular particle of embedded sand impinging on the superficial pain nerve endings.

We then had a cure. Under local anesthesia, using a Gillette® Super Blue Blade, we tangentially excised the epidermis of her fingertips, removing all of the embedded particles and hence, the source of her pain. This required no sutures and the skin healed rapidly. Our patient was soon back at work doing "thirty heads" a day with the old-fashioned curlers. It was not very long before the new silica hair curlers were off the market. And we think her "new fingertips" launched a thousand referrals to our office.

QUESTIONS FOR THE DOCTOR:

- Could there be foreign bodies in the fingertips, such as fragments of steel wool used in dishwashing?
- Could the tenderness be due to exposure to Clorox ® or paint solvents?
- Has the patient ever had frostbite of the fingers?
- Does the patient have dry skin with multiple tiny fissures?
- Does your patient work with sand?

16

A STRANGE SUNBURN

"I can't stand the sun. It burns me," was a seventy-eight-year-old man's complaint. We thought this would be just another case of photosensitivity due to medicine he was taking. But, that is not how it turned out.

For many years he had completely avoided sunlight, because even being in the sun for a few minutes made his exposed skin itch and burn and turn bright red. It was no ordinary sunburn, which takes hours to develop, but was virtually immediate. By going indoors the reaction would pass in about an hour, leaving no trace. He had never been outdoors long enough to know how severe a burn he might develop.

His history disclosed that he had had an adenocarcinoma of the colon excised two years ago. Otherwise, he had always been in good health. He had no known allergies nor did he smoke, drink, or take a single medication. His family history was noncontributory. His contactants included Dial Soap, shaving cream, after-shave lotion, baby shampoo, and a hair colorant.

He had found sunscreens and antihistaminics of no help. Physicians had tried a number of prescriptions without success.

On examination his skin was normal, but when we sent him outdoors for ten minutes of exposure to the February sunlight, he returned with extremely red skin over his hands, face, neck, and scalp, which burned and itched severely. He remained in our office for the afternoon while his symptoms and the redness abated. At the next visit, we reproduced his burn and pain with four minutes of ultraviolet light exposure in our light box. By contrast, significant exposure to intense white light was tolerated.

Why this amazing sun sensitivity? After his physical and routine laboratory studies were normal, we rounded up the usual suspects. No, it was not the colon cancer. X-rays showed it was gone and this was confirmed by a normal CEA level. No, it was not a porphyrin photosensitivity. His blood and urine porphyrins were normal. He did not have a porphyria in which the chemical building blocks for hemoglobin were in excess. No, it was not the drug photosensitivity we see frequently from medications taken by the elderly for arthritis or high blood pressure. He took no medicines.

Well, how about a contact photosensitivity? Yes, here was where the answer lay. There are numerous chemicals, as well as plants which, when in contact with the skin, may sensitize the patient to the sunlight. These range from limes to celery, and from sunscreens to colognes. So, we put thirty compounds on his back under a taped covering for forty-eight hours. After removing them, we exposed his back to tubular fluorescent lights. Then came the answer. The spot where a 2% formaldehyde solution had been applied immediately became a vivid red. He was formaldehyde photosensitive. All the other tests were negative.

Our success in finding the cause of his strange sunburn was not matched by success in therapy. Chloroquine, the sovereign remedy for sun sensitivity, had no effect nor did beta-carotene, which increases most patient's sun tolerance. Having him eliminate formaldehyde-containing permanent press clothing and sheets also didn't help.

Formaldehyde is ubiquitous. It is not only in clothing, but also in shampoos, cosmetics, mouthwashes, paper, detergents, disinfectants, insecticides and cigarette smoke. It can even "come out of the woodwork," as lumber and insulation are being formaldehyde-treated. Our patient has no place to hide from formaldehyde, but hide he must from sunlight and the tanning booths.

QUESTIONS FOR THE DOCTOR:

- Is your patient taking any photosensitizing medications (e.g., thiazide diuretic, nonsteroidal anti-inflammatory drug, or tetracycline)?
- Could your patient be allergic to a sunscreen?

- Could the photosensitivity be due to exposure to a perfume, soap or aftershave lotion?
- Does your patient work around celery on a farm or in a store?
- Have you checked for porphyrins in the patient's blood and urine?
- Has your patient had a gastrectomy?
- Is your patient an alcoholic?
- Does your patient have an adequate diet or could he have pellagra?
- Have you checked an ANA?
- Have you given the patient a trial of oral nicotinamide?

17

A MULTIPLE PERSONALITY DERMATITIS

"Look at my arm. It's all messed up," opened our consultation with a twenty-eight-year-old woman. And we did look. What we saw was a left arm swollen to three times its size. We saw not only a hand, but a forearm and upper arm completely denuded of the outer skin. The entire limb was dusky red in color, and oozing clear fluid that dripped on the floor. Four physicians had seen her in the four weeks since it had all started. None could help despite intensive cortisone therapy and steroid salves. Day by day the problem had worsened.

This called for immediate hospitalization, for both therapy and diagnosis. Her history did not help. She had always been in perfect health. The only skin disease she had ever had was poison ivy dermatitis in her childhood.

We were worried that she had suffered a blood clot in her arm, but the vascular surgeons found nothing wrong. A Doppler study confirmed that she had normal circulation. Then began a circus of consultations and laboratory studies. During her three weeks in the hospital, she was seen by a parade of internists, anesthesiologists, and psychiatrists.

We kept the arm wrapped in compresses, and the anesthesiologists provided nerve blocks to improve circulation. The dermatitis gradually subsided and the arm became less swollen. But on day three, and again on day fifteen of hospitalization, we came in to find a huge soft purple swelling on the back of her left hand. Each time we drew out almost an ounce of blood from these swellings, which were hematomas.

The psychiatrists cleared the way for our understanding the nature of this worst dermatitis of the arm we had ever seen. Our patient had

multiple personalities, each having their own name. The psychiatrists could identify six, but on rounds we saw only three:

1. An unhappy, petulant, pouting little girl four years of age who sat on the floor and begged to leave the hospital.
2. A belligerent dominant macho-type Marine Sergeant.
3. The primary patient.

The other three personalities observed elsewhere were an aged grandmother, a sexy seductive teenager, and a college student. On deeper questioning, the patient gave a history of a chaotic childhood in which she was the victim of bizarre psychic abuse by a psychotic mother.

By three weeks, we had the most remarkable history we had ever taken. The dermatitis had begun five weeks ago when the "Marine Sergeant," wearing a rubber glove on "his" right hand, rubbed her left arm with fresh poison ivy leaves "he" had gathered on her home grounds. This was repeated every single night, with the leaves applied under an elastic bandage. Hence, the rest of the body never developed any blisters or rash. Once in the hospital, the "Marine Sergeant" no longer had access to the poison ivy plants and turned to banging her left hand on the steel chair in her room, thus explaining the two huge hematomas full of fresh blood. She was discharged from the hospital healing well and the "Marine" was told never to touch poison ivy again, because he might become allergic and put everyone at risk.

The follow-up is that the next time we saw her she was on the front pages of our city newspaper. She had been shot in the lower legs by a robber (Marine Sergeant?) who broke into her employer's home and stole the silver tableware. She was a heroine, until caught on crutches trying to peddle the silverware to a "fence" in another city. Her lawyer pleaded "multiple personality" as her defense.

Few medical problems have attracted as much attention as the multiple personality syndrome. The concept that more than one "person" may exist in one body is so foreign to common sense that it is in the twilight zone of the supernatural. But, rare as it is, it is not simply fictional, as in the case of Dr. Jekyll and Mr. Hyde. Some 200 patients have been reported, and undoubtedly even more have been sighted. Three have reached biographical eminence as Eve, Sally, and Sybil, in both books and films.

Psychiatrists classify the problem as a dissociative hysteria, which is a type of neurosis. Others feel these patients are deluding us by parading forth a variety of characters in a consummate theatrical performance.

The nature of our patient's self-induced factitial dermatitis, as well as her psychiatric state, was clearly unrecognized and unsuspected by the first five physicians consulted. Only hospitalization and close observation solved this mystery.

QUESTIONS FOR THE DOCTOR:

- Have you hospitalized your patient for close observation?
- Does your patient experience fugue states?
- Could your patient be trying to deliberately baffle her physicians?
- Does your patient sometimes feel like another person?
- What does the patient think is causing the skin problem?
- Has the patient ever been evaluated by a psychiatrist?

18

ACCIDENTAL HIVES

"Did these hives come from my truck accident or didn't they?" asked a twenty-eight-year-old man. Five weeks before the hives appeared he had almost been killed in a truck accident. Now, a year later, the hives continued. We did not know the answer to his question, but were eager to find out. His hives were the most unusual we had ever seen. They were small red mosquito bite-like swellings, but each was surrounded by a remarkable halo of white blanched skin.

We were familiar with cholinergic urticaria, small hives resulting from heat, exercise, or emotional stress. But, these hives have halos of redness, not blanching. They result from an abnormal sensitivity to the neurotransmitter, acetylcholine. Injection of this chemical into the skin exactly reproduces the small hives with red circles. When patients say their hives are the result of "nerves," we are usually skeptical, except for this, the only authentic example. For most patients hives are not due to nerves, but result from an allergic response to any one of a thousand allergens. Our patient did not have cholinergic urticaria. He had white halo hives, not the red halo-type due to acetylcholine release from stress, heat, or exercise.

Yet, could his hives also be due to nerves, perhaps with a different neurotransmitter? No one had ever described such hives, yet his history clearly implicated "nerves" as a possibility. His truck accident left him with a morbid fear of driving. After his hospitalization for major facial injuries from the accident, he was found on psychological testing to have post-traumatic stress disorder. He could not drive and frequently awakened at night reliving the plunge through the truck windshield. The very sight

of his truck at the work place brought on an attack of hives within ten minutes, which grew into giant welts covering large areas. At times, he also experienced difficulty in breathing. Soon after the accident he noticed his hands were losing their pigment. This was vitiligo, again a disorder associated at times with the autonomic nervous system's response to stress.

Finally, attacks of hives could be brought on by coffee or chocolate intake. Here, the discharge of adrenaline could be suspected of playing a role. But adrenaline is what we use to treat hives, as it effectively constricts the leaky vessels responsible for hives. Surely, it could not cause hives, or could it?

For months we struggled with his hives. His health was good; his blood and urine studies were normal. Blood levels of histamine, a major agent in producing hives, were normal taken before and during major attacks of hives. But, we found that during a major attack, his blood levels of both adrenaline (the stress hormone), and norepinephrine (the neurotransmitter for sympathetic autonomic nerves), had increased twofold to fivefold. These two compounds differ very little. The one coming from the adrenal gland is adrenaline or epinephrine (epi – upon; nephron – kidney, i.e., the gland adjacent to the renal organ). The one discharged from the nerve endings is norepinephrine or noradrenaline.

We could see that these chemicals were being released during the episodes of hives. On skin biopsy we found that the mast cells were discharging, presumably releasing their histamine to cause the hives. It seemed likely that a sensitivity to norepinephrine triggered the mast cells to degranulate and spill out histamine. The patient's blood also revealed that he had a high level of the protein, immunoglobulin E (IgE), responsible for allergic reactions. This favored the possibility of an immune reaction. It now seemed plausible that our patient may have become sensitized to the neurotransmitter, norepinephrine, just as certain patients become sensitized to another neurotransmitter, acetylcholine. This would mean that when his sympathetic nerves were excited by stress, norepinephrine was released that combined with IgE protein on the mast cell surface, releasing histamine.

But norepinephrine usually blocks the action of histamine and the formation of hives. How could it possibly be the cause? We found the answer by thinking small . . . very small. When we therapeutically inject the usual dose of norepinephrine into the skin to stop hives, it is diluted to 1:10,000. The skin turns totally white and no hive can form at that site.

But when the nerve releases norepinephrine, it is only a few molecules, which could trigger allergy without constricting the vessels enough to prevent the histamine effect. Yes, that was the answer. We were able, in this patient, to duplicate his hives by injecting extremely small amounts of norepinephrine into his skin, diluted 1 to 2 parts per million. The mosquito-bite hive appeared at the injection site, complete with the surrounding diagnostic ring of pallor.

We had discovered a new disease and named it adrenergic urticaria. Once we realized that patients could be "allergic" to adrenaline, and noradrenaline, we understood why, in the emergency room, some patients with hives get much worse when given the standard adrenaline shot. Such mishaps can be avoided if the attending physician checks for the diagnostic white halo hives as seen in our patient. And we, in our practice, could confidently tell patients that if they did not have the white halo or the red halo hive, their hives were *not* due to nerves.

With new understanding of the origin of our patient's hives we were able to control them by prescribing a drug, propranolol, which blocks the receptors for norepinephrine. He has been virtually clear of hives for over one year now. When the propranolol was stopped for seventy-two hours, his hives reappeared. He still avoids coffee, chocolate, and his truck!

QUESTIONS FOR THE DOCTOR:

- What does the patient think caused the hives?
- Have you observed tiny hives with white haloes?
- Do the hives appear when the patient gets nervous?
- Are the hives made worse by eating chocolate or drinking coffee or other caffeine-containing drinks?
- Have you prescribed a trial of oral propranolol for adrenergic urticaria?
- Have you done an intradermal skin test with norepinephrine?

19

THE ODOR OF ROTTEN FISH

It wasn't the patient complaining, it was the nurses! The nurses and staff complained of the odor of rotten fish permeating their entire hospital floor. Some days it was overwhelming, but some days it was not there, coming only episodically, but several days a week. It was not hard to track down the source. It came from a thirty-one-year-old man institutionalized with severe mental retardation, and it came from his urine as well.

We at once suspected that this man had the *"fish odor syndrome,"* because years before we had encountered a twelve-year-old boy with this same foul odor. He had been virtually ostracized from school and society, because no amount of bathing, oral hygiene, or deodorant powders helped. Every breath repelled his friends. Otherwise, he was healthy, normal, and attractive.

But this patient was a tragic victim of a toxemic pregnancy and multiple abscesses in infancy. He still could not walk, talk, or raise his head when he was six years old. Institutionalized nearly all of his life, he had an IQ of 5 and a mental age below six months.

Physical examination disclosed a unique individual who had massive folds of skin on his forehead and soft skin that could be stretched out for inches. He kept hitting the sides of his head and was generally self-abusive. There was a strong fish odor present. His blood studies were normal.

But did he have the fish odor syndrome? To find out we needed a laboratory to analyze his urine for the gas, trimethylamine, which has the odor of rotten fish. None of the hospital or commercial laboratories could do this, but we located a research facility at the University of Colorado who performed the necessary gas chromatography. They reported back

that his urine had a high level of this odoriferous amine, which is totally absent in normal individuals. He thus qualified as an authentic example of that rare entity, fish odor syndrome, i.e., *trimethylaminuria*.

But, what was the source of this fish odor? Most odors in and of the body are caused by bacteria. Indeed, the odor in the armpit is the result of bacteria growing in the apocrine sweat of that area. The odor of foul breath is usually due to bacterial growth accompanying poor oral hygiene. Foot odor is from bacteria growing on sweaty feet. And the foul odor of some skin ulcers, again, is from bacteria, usually the anaerobic types that grow in the complete absence of oxygen.

So, it was no surprise to find that the odor of our patient was also produced by bacteria. In this case, the rotten odor of trimethylamine was generated in the gut by bacteria acting on food. All of us have this gas bubbling in the gut, but normally the liver oxidizes or changes it to a nonodorous oxide. In this patient, however, and in all those with fish odor syndrome, there is a defect in the liver enzyme oxidizing this odorous amine. Consequently, this rotten fish amine travels through the blood to come out through the skin, urine, and breath.

What is it in food that the bacteria feast on to produce the trimethylamine? It is a simple chemical, choline, a prominent component of egg yolk, liver, soybeans, and, of course, fish. By simply eliminating these, including mayonnaise, from our patient's diet, it was possible to deodorize his hospital ward for the most part. The occasional "gas attacks" were abolished finally by eliminating the responsible bacteria in the gut with a two-week course of Flagyl® (metronidazole). Later, we learned that eating *Brassica* vegetables (brussel sprouts, cabbage, broccoli, cauliflower, turnips, and mustard) will also promote the odor, because they have chemicals that compromise the liver's ability to oxidize the malodorous gas coming from the gut.

The genetic deformities of this poor man have extended to his liver function. We could do little to change this, but by dietary manipulation and bowel sterilization we made the hospital habitable again. What's in the skin often reflects what is within.

QUESTIONS FOR THE DOCTOR:

- Have you ever detected the odor on your patient?
- Has anybody other than the patient detected the odor?
- Does the patient describe the odor as "rotten fish" or something else?
- Have you tried to confirm the diagnosis of trimethylaminuria using gas chromatography?
- Have you prescribed a low-choline diet with particular emphasis on avoiding eggs, soybeans, peas, liver, and fish?
- Has your patient applied any topical products (e.g., shampoo) containing chemicals similar to trimethylamine?
- Does your patient eat a diet high in Brassica vegetables (broccoli, cauliflower, cabbage, and/or brussels sprouts)?
- Does the odor appear after the patient drinks milk?
- Have you prescribed a trial of oral metronidazole to alter the gut flora responsible for producing trimethylamine?

20

HORMONAL BLISTERS

Sometimes despair over a skin disease that fails to yield to treatment can lead to suicide. We have seen that tragedy twice – once in a young man with hair loss and the other in a boy with acne. And it almost happened with this patient. For five long years, a twenty-seven-year-old woman had suffered an extremely severe itch associated with small water blisters on her arms, legs and trunk. They came in groups in arciform configuration. Many of the soft tops had been scratched off, leaving areas of redness, crusting, and scars where she had dug the skin away to relieve her itch. The skin was both hyperpigmented and depigmented.

She stated that it all began a week after the birth of her second child. She was told it was due to sunlight sensitivity, and, indeed, it slowly faded as she dutifully avoided the sun. Two years later it recurred explosively after the birth of her third child and then had remained unchecked for the past three years. She has wandered from doctor to doctor, who have wandered from diagnosis to diagnosis, and from treatment to treatment. She has had numerous biopsies and as many diagnoses. Steroids, antibiotics, antihistaminics, and sedatives were all of no avail. She was told it was due to nerves, that it was due to an allergy to gluten in wheat, and that it was a virus infection. AIDS had not made its entrance or it, too, would have been considered. *She was an orphan patient*. But one thing she knew for certain was that her itch and water blisters always got worse before her menstrual period. The other thing she knew was that she was having dark thoughts of suicide.

When she was referred to us we knew that immediate hospitalization was necessary, for both her own safety and for our detailed diagnostic tests.

We were impressed by her primary observation. "It's so much worse before my period." But this struck no diagnostic chord for we knew that many skin diseases worsened before the menstrual period. We had seen it repeatedly in patients with acne, psoriasis, lupus, eczema, and rosacea. Indeed, some of our patients experienced an outbreak of cold sores before each and every period. Premenstrual flares were assumed to result from an alteration in a woman's immune status. But as our studies were to show, this was not the case in this patient.

As we studied the clinical findings, we were left baffled. We felt it could be any one of the following eight diseases:

- dermatitis herpetiformis
- lupus erythematosus
- bullous lichen planus
- drug eruption
- factitial dermatitis
- trichophytid
- porphyria cutanea tarda
- bullous erythema multiforme

Blood and urine studies gave no leads. The urine studies proved it was not porphyria. A blood test ruled out lupus. Challenges with her drugs gave no flares. The failure of dapsone to help eliminated dermatitis herpetiformis. A biopsy ruled out lichen planus and the trichophytid diagnosis was dropped when skin tests to fungi were negative. Finally, as we got to know the patient in the hospital we just knew she was not a case of self-mutilation, i.e., *factitial dermatitis*. The skin biopsy findings fit the diagnosis of bullous erythema multiforme, an entity with numerous causes.

As we continued to muse, the question came up, could this women be allergic to her own hormones, specifically progesterone, which climbs to high levels each month just before the menses? With trepidation we gave her an injection of progesterone. Within a day new blisters covered her skin and a blood test showed that the basophil leukocytes in her blood had all degranulated, a sure sign of an allergic reaction.

Skin tests to a variety of other agents were negative, so we felt assured she was truly an example of progesterone sensitivity.

Parenthetically, that progesterone injection initially induced a profound, yet temporary, depression within hours. It was a dramatic example of the mood changes induced by the elevated progesterone levels that may occur premenstrually.

We tried to desensitize her to progesterone, but injections of progesterone, small as they were, only made her itch more and caused her

blisters to get much worse. We turned to suppressing ovulation with the hormone, estradiol. By suppressing the source of the progesterone, that is the ovary, we had instant success. But whenever we stopped the estrogen to permit menstruation, the dermatitis roared back. Finally, we had the surgeons remove her ovaries. They were histologically normal and in ten days the patient was totally free of her itch and blisters. She has had no return in the subsequent years.

Once described by us, autoimmune progesterone dermatitis has taken its place in the dermatologic literature. An ever expanding variety of lesions has been recognized, from hives to hand eruptions, and today most are successfully treated with the drug, tamoxifen.

QUESTIONS FOR THE DOCTOR:

- Do the blisters get worse before her period?
- Is your patient taking any female hormones?
- Does your patient use any estradiol-containing vaginal creams or inserts?
- Does your patient apply any estrogen patches?
- Does your patient take birth control pills?
- Does your patient take any "morning-after" pills?
- Has your patient had a trial of therapy with tamoxifen?

21

FLOWER SHOP ITCH

"I itch and I know it's my work." But what caused his work itch? A twenty-one-year-old man showed us a very itchy red rash on his forearms, lower legs, and eyelids. It had started twelve days before, within hours after returning from vacation to his job in a wholesale florist supply shop. The rash had become worse every day and was now so severe that he had missed work for the past six days.

He had worked in this shop for six years, with only one previous attack of dermatitis, four months ago. No cause had been found for the rash, and it had responded to steroid injections from his family doctor. The patient was in good health, but had known sensitivities to poison ivy and bee stings.

Originally, he had had small blisters, but now only scratch marks remained on his inflamed skin. We suspected an occupational dermatitis, because he had not been exposed to poison ivy on his vacation. He remained off work for four more days. Back at work he was fine the first day, but the next day the itch became worse and was especially severe in the finger webs.

We saw him a week later, when our scrapings of the fingerwebs ruled out scabies. He denied all exposure to solvents, harsh soaps, fiberglass, and epoxy resins, but did have to handle a wide variety of plants at work. He had a dog at work and a cat at home, but neither animal had any dermatitis or itch.

We knew that florists commonly have hand dermatitis due to tulips and chrysanthemums. In fact, we remembered a woman with chronic hand dermatitis who worked in a florist shop telling us she had seen a doctor

just once, eight years ago, for her hand eczema. The doctor had prescribed cortisone, and friendly pharmacists kept refilling that prescription for eight years to keep her from losing her job. She had developed all the known side effects of long-term cortisone, from hypertension to peptic ulcer, as well as osteoporosis and purpura. Our patch tests showed she was sensitive to chrysanthemums. Avoiding them permitted her to avoid more cortisone, with its side effects gradually fading away.

Our young man had dozens of potential other causes for his dermatitis. Patch tests with a variety of allergens showed no sensitivity to flowers. However, intradermal tests revealed marked sensitivity to house dust mites, but a negative flea antigen test. When we treated his entire body with Kwell® (lindane) lotion, he got complete relief.

We did not see him again until a month later, when he had his third attack of itching and dermatitis. This time he correlated his itch with the arrival of several hundred Hagnaya wreaths from the Philippine Islands. The itch began the same day he began unwrapping and unpacking these dried decorative wreaths, made from twisted dried vines of a fern of the Polypodium family.

Could he be sensitive to this vine? No, because patch tests to this and twenty common contact allergens were negative, except for thimerosal, with which he had had no current contact. Could it be due to mites? Again, none were found in the scrapings of his skin. However, microscopic examination of the leaves of the plant showed not only mites, but also their eggs. Because there are more than 400 families of mites known, identification was difficult. But the Acarology Laboratory at Ohio State University identified no less than seven genera of mites in the wreath specimens we sent.

Ten days after avoiding the wreaths our patient was cured. Interestingly, once the wreaths were removed from the shop, a similar, but milder, eruption in two of his fellow employees also cleared.

Of all the mites found on the wreaths, the only one likely to have caused the dermatitis was *Cheyletus malaccensis*, well known to cause a pruritic dermatitis in man. Our patient's experience is only one of many occupational mite-induced skin problems that are seen. The hay ride straw itch, grain itch, grocers' itch, and bakers' itch are a few examples. Cheese, figs, and cottonseed itch are also known. We have also seen mite itch in a woman making dried wheat floral arrangements.

Always, the diagnostic secret is to look not only on the skin, but to examine the surroundings. These mites "bite and run." You usually do not find them on the skin.

The fact that one of us developed an itch by simply handling the wreath brought to our office made it very likely that hundreds of wreath hangers from coast to coast suffered with unexplained itching that Christmas.

QUESTIONS FOR THE DOCTOR:

- Does the patient think the itching is due to his work?
- Does he work with fiberglass?
- Does the patient have pets (dogs, cats, rabbits, birds) that could harbor fleas or mites, and are any of the pets itching?
- Does the patient work with plants, which could harbor mites?
- Does the patient work with any toxic chemicals or sprays?
- Have you done scrapings of the skin lesions looking for mites and fiberglass spicules?
- Have you examined any of the suspect plant material for mites?
- Does your patient handle any imported Hagnaya wreaths?
- Does your patient live in a house with bird's nests in the eaves or attic?
- Has the patient had a problem with carpet beetles in the house?
- Has the patient had his house treated by an exterminator?
- Has the patient's work area been treated by an exterminator?
- Has anybody else at home or at work been itching?
- Has he had an intradermal mite antigen skin test?
- Did application of a topical scabicide relieve the itching?
- Have you prescribed a trial of oral ivermectin?
- Did removal of the suspect plant material from his work environment improve the symptoms?

22

"STRESS AND A PENNY" HIVES

"I get hives when I get overheated" was the complaint of a thirty-year-old woman. But the problem was more complex than this. Unraveling her lengthy history we learned that the hives came out not only from being in a hot room, but also whenever she took a hot bath. Furthermore, she suffered from attacks of intense flushing of her skin. All this could be brought on also by emotional stress. Even exercise triggered her problem. She had suffered these attacks for six years without relief, and they were increasing in severity and frequency. In the past year during attacks she had experienced intense itching of her entire skin, along with feelings of weakness, headaches, and palpitations. She had consulted many doctors and taken a wide range of medications without help.

The gravity of her problem demanded hospitalization for complete analysis. With blood studies we were able to rule out the two rare tumors known to produce episodic flushing, carcinoid and pheochromocytoma. A strict elimination diet and avoidance of all medications also did nothing to lessen her attacks. Day by day, as we weathered her attacks with her, we realized her lesions began as hives with tiny red halos, characteristic of so-called "cholinergic hives." In such cases patients become sensitive to acetylcholine, a chemical released from sympathetic nerve endings in times of stress. This compound also causes blood vessels to dilate, which leaves the skin with a red flush. But, we had never seen such a severe case and realized that her sensitivity to acetylcholine must be extremely high. When we injected into her skin trace amounts of this neurotransmitter (acetylcholine chloride $1{:}10^{-3}$), her skin lit up with local hives

and flushing. A biopsy showed that the acetylcholine had discharged the histamine from all of her mast cells in the skin, thus inducing hives and flushing. But other tests showed she was not supersensitive to histamine, nor did she have an excessive number of mast cells in her skin, the cells that make histamine.

The fault was actually a supersensitivity to acetylcholine. In special skin biopsies we found that she had enormously increased numbers of receptor sites for acetylcholine, thus making any release of acetylcholine much more powerful than it would be in normal skin.

As we continued to probe her history, separating the golden relevant from the dross, we learned that the severity of her attacks had a monthly periodicity. They were worse before her menstrual period. But skin tests to several female hormones failed to show them as a cause.

Finally, we learned that she had had a copper intrauterine device (IUD) inserted two years before her hives had begun. Although it had been removed several years ago to see if it was the cause, her hives had continued. But now we had a true lead. Could copper be the material making her so sensitive to the acetylcholine released by her nerves? If so, we felt that removing the copper IUD was not enough, because she was still being exposed to copper ions released from the copper in her dental fillings.

And so it was! We were able to prove she was sensitive to copper. Simply taping a copper penny on her skin for forty-eight hours, then removing it and having her exercise, brought out a hive at the penny site. She was not actually allergic to copper, as the skin had looked completely normal where the copper penny had been, prior to exercise. But, copper ions had obviously entered the skin and made that spot sensitive to acetylcholine. We confirmed this phenomenon with a patch test using pure copper sulfate solution. Again, there was no visible allergic reaction seen, only a remarkable hive on that spot after she became overheated.

Now we suspected that the cure could come with removal of all of her dental fillings. This was not done due to the expense, but she had considerable relief just knowing how her nerves triggered the attacks. By avoiding hot baths, hot rooms, and hot spots, and by staying cool mentally and physically, she is no longer a victim of the fear of the unknown. She has also been helped by avoiding copper in sprays and fumes, as well

as taking anticholinergic and antihistamine drugs. She has been able to control the three beasts – copper, acetylcholine and histamine – that had ruined her life.

Here was an orphan patient with a serious skin mystery who had had a *tour de force* workup that included twelve skin biopsies, over 100 laboratory tests, and innumerable skin tests during her hospitalization. But, it was well worth it to have a penny for our thoughts.

QUESTIONS FOR THE DOCTOR:

- Does your patient get hives when overheated?
- Does exercise and sweating bring on the hives?
- Are the hives widespread and mostly large or small?
- Do the hives have red haloes?
- Did you do an intradermal skin test for acetylcholine?
- Have you actually observed the hives by having the patient vigorously exercise?
- What does the patient think causes the hives?
- Has the patient had a complete dental exam searching for infection?
- Does the patient have dental amalgams?
- Do any foods seem to contribute to the problem?
- Could your patient be allergic to copper?
- Has your patient ever had an IUD containing copper?
- Have you checked her blood for eosinophils and serum IgE?
- Have you taken a complete drug history?
- Are the hives worse before her period?
- Have you done intradermal skin tests for estrogen and progesterone?

23

THE CASE OF UNILATERAL WRINKLES

"My friends tell me I'm growing old, but only on one side" was the complaint of a sixty-two-year-old woman. And her friends were so right. This woman, in her sixties, had the aged wrinkled appearance of a woman in her eighties, but only on the right side of her face, the right side of her neck, and her right hand. She had not always looked that way. Over the past year she had noticed the one-sided wrinkles appearing asymptomatically and insidiously. There had been no prior redness, swelling, or pain nor had she had any episodes of toothache, sinusitis, or parotitis (inflammation of the parotid gland), or any other infections. She had never had any trauma to the area, radiation therapy, or unusual ultraviolet light exposure to her skin (in or out of automobiles). She had never had any skin disease. There was no family history of premature aging or wrinkling of the skin. Her health had been excellent.

On close examination the affected skin, especially over her right cheek, was thin and loose, hanging in numerous deep wrinkles. The underlying fat layer felt reduced in thickness. The skin of the left side had the normal appearance for a person her age and was essentially without wrinkles. Neither side showed the aging spots or keratoses of sun damage. The skin on her right wrist and hand also had an aged wrinkled appearance. The covered parts of her body did not show any wrinkling.

We found the answer to her one-sided aging under the microscope. On the wrinkled side, the elastic tissue was relatively sparse and fragmented with very few of the long branching elastic fibers that kept her skin taut on the left side. Moreover, on the affected side the large blood vessels showed no evidence of the internal elastic membrane so essential to control blood

flow. In contrast, the vessels on the left side had the normal resilient elastic component of the thin walls. Other aspects of the skin architecture were the same on the two sides, except for some diminished size in the fat compartments under the dermis of the right side, with the fat cells thin and stretched.

The aged appearance of the right side of her face aroused interest only on comparison with the other side. At once she had the profiles of two sisters, widely separated in age. If both sides of her face had had identical wrinkles, she would have been diagnosed as having a familial trait with degeneration of elastic tissue fibers and loss of subcutaneous fat. She would then have been a good candidate for Retin A®, α-hydroxy acid therapy, laser surgery, or a face lift.

Only by having an individual who served as her own control could we perceive the vital role that the elastic mesh was playing. To understand her "hemirhytides" it is necessary to be aware of the special nature of facial skin. Here is skin that responds to every movement of the facial muscles with a smile or a frown. This felicity of response so essential in a primitive world signals friend or foe and is essential to reflex action. It is all achieved by the presence of a remarkably complex and dense mesh of elastic tissue woven into the fibers of inert collagen. This invisible "sheath" of elastic tissue is unique to the face. With aging comes loss of both the elastic and fibrous collagen tissue, induced mainly on exposed areas by years of damage from the sun's ultraviolet rays. It is these rays that destroy the elastic fibers, which are the moorings that hold our skin firm.

Since photo-aging is symmetrical, we can assume that our patient was born with a poor supply of elastic fibers on the right side. This congenital asymmetry of elastic tissue remained inapparent until the marginal reserves on her right side were depleted by sunlight damage. Only then did the unilateral facial wrinkling begin to appear. Sometimes, a congenital defect becomes evident only after a lifetime of stress and strain.

The absence of elastic tissue in the walls of the large vessels was the most unexpected and alarming feature we found. This weakness could forewarn of an aneurysm or rupture in the blood vessel wall. She must not be allowed to develop high blood pressure.

Unfortunately, we do not yet know how to grow elastic tissue in the test tube or tissue culture. A scar is filled with collagen, but no elastic fibers. And so, a hemi-face lift probably would be this patient's best cosmetic venture.

QUESTIONS FOR THE DOCTOR:

- Has your patient spent a lot of time in the sun, leading to chronic actinic damage of her skin?
- Does your patient usually ride as passenger in the right side of the front seat of a car, thus increasing exposure to sunlight on the right side of her face?
- Have you done a skin biopsy with special stains for elastic tissue?
- Did your patient have a rash prior to onset of her wrinkles?
- Is there any family history of unusual facial wrinkling?
- Has your patient treated her wrinkles with Retin-A® (tretinoin)?
- Would your patient benefit from laser surgery, collagen injections, or a face-lift?

24

FIERY RED LEGS

"Look at my legs" said a thirty-nine-year-old woman. We looked and in a split second knew the diagnosis. It was one of the *augenblick* diagnoses a dermatologist makes in 1/25 of a second when a recognizable pattern of skin disease is present. For these diagnoses, it is better to pass by a dermatologist in the hall than spend hours in a general physicians office or have a sheath of laboratory reports. Specialism has its place. A specialist does not have to re-invent the disease.

Yes, she had essential progressive telangiectasia, made up of innumerable tiny dilated blood vessels extending up her legs. We do not know the cause, but have seen them cover the entire body, becoming generalized. No, the mystery here was not the diagnosis, but why did she have it, and what could we do about it?

First, as always, there is the history. Seven years before she first noted a red patch of small dilated blood vessels over her right foot. It seemed innocent enough, perhaps due to a tight fitting shoe. But soon it appeared on the other foot, also due to a tight shoe? Then she became alarmed as this fiery red eruption began to climb up her legs. True, it was not painful, itchy, or bleeding, and there were no black and blue marks. No one else in the family had anything like it.

The dilated (telangiectatic) vessels had reached her thighs by the time she reached our office. She had not ignored their inexorable ascent, having seen many doctors. They had tried to reassure her that she was healthy by doing many laboratory examinations, but had nothing at all to offer for explanation or treatment.

She still had that *bête rouge*, and feared that eventually it would embrace her entire body. Examination revealed numerous small vessel

telangiectases in a fiery red skin, which were most prominent on her feet and ankles. They extended up both legs onto the thighs, completely encircling her limbs. There was no swelling of the skin, or any enlarged or varicose veins. The pulses were normal, as was the Doppler test for circulatory defects. Color changes on raising and lowering the legs were normal, ruling out arteriosclerosis. Cutaneous sensation and ankle and knee jerks were intact.

Biopsy of the skin showed innumerable dilated capillaries throughout the dermis. The rest of the skin was normal, including the elastic tissue. We had now clearly confirmed the diagnosis, but what to do?

Textbooks and medical journals gave no help for this orphan disease without a treatment. We therefore approached therapy by analogy. The fiery red skin of her legs, if transposed to her face, would be called rosacea. Accordingly, we prescribed our favorite rosacea treatment, oral tetracycline, for her "leg rosacea." Within a few weeks distinct fading of the telangiectasia could be seen. After three months all of the small telangiectatic vessels and diffuse redness was gone. We cut the dose of tetracycline in half and continued it for another six months. There has been no recurrence.

We suspect this antibiotic eradicated a focus of infection somewhere in her body. Foci of infection are known to elaborate blood vessel growth hormones. The best example is seen in the highly vascular pyogenic granuloma ("proud flesh"), which arises at the site of an infection. More recently, blood vessel tumors have been seen in AIDS patients, coming from an infection called "bacillary angiomatosis."

For every unexplained skin change there is an undetected cause. Answers come to those who think, look and act. Orphan patients deserve no less.

QUESTIONS FOR THE DOCTOR:

- Has a skin biopsy been done to confirm dilated capillaries and rule out angiosarcoma?
- Does your patient have a smoldering chronic infection, such as sinusitis?

- Is there a history of recurrent vaginal yeast infections?
- Did you do an intradermal *Candida* skin test?
- Did you obtain photographs, diagrams, and measurements on the legs to document the extent of telangiectasia as a baseline for evaluating the effectiveness of future therapy?
- Have you prescribed three-month trials of various antibiotics (e.g., tetracycline, minocycline, clarithromycin, ciprofloxacin, or metronidazole) and antifungals (ketoconazole, itraconazole) to see if the progressive upward spread of the telangiectasia could be halted?
- Does your patient want a trial of laser therapy?

25

PAINFUL FEET

"My feet hurt," said a twenty-year-old college student. We wondered, could he be in the wrong office? Shouldn't he be seeing an orthopedic surgeon, podiatrist, or rheumatologist? But no, since these other physicians had shunted him off, he came to see us as an orphan patient.

As he was lying disrobed on the examining table, we saw only perfectly normal skin on his feet, as well as elsewhere. At least we could tell him he had no suspicious-looking moles or melanoma. But, we listened to his story. He had never had any problem with his feet until this summer when he went to work as a railroad trackman. He wore comfortable proper-fitted shoes, yet within a week of starting work his feet had become painful. He had continued to work until he saw us.

The feet seemed normal. They had never been injured. There were no tender spots. Motion was normal, both passive and active. Complete vascular assessment was unrewarding. We contemplated getting x-ray views of his feet to check for the presence of bone spurs. We also heard him say repeatedly, "It only hurts when I stand for a long time." Could this be a paresthesia from pressure on the sciatic nerves? The answer came when we asked him to get off the table and stand up. Immediately on standing, firm bumps appeared on the medial aspect of both heels. They slowly disappeared once he was off his feet, but we could bring them out again by applying firm pressure on his soles. They were not hives, since they came up instantly.

The answer was in the skin biopsy. They were hernias, cutaneous hernias. In this case, ruptures in the overlying fascia caused herniation of fat into the upper skin, along with its blood and nerve supply. They were truly diminutive versions of the inguinal or umbilical hernias where the

gut slips out through the overlying fascia. After a period of time hernias became painful as blood vessels and nerves become compromised by being squeezed into an unyielding compartment.

We had not seen such hernias before, nor were they in the ken of diagnostic tests. The closest we could come in the literature were fat hernias of the perianal area, recognized by proctologists, and fat hernias of the lower eyelids, seen by ophthalmologists. We had discovered a new entity, and christened it alliteratively, *painful piezogenic pedal papules*. "Piezogenic" means induction by pressure. We now know that a painless version is quite common.

We further studied our patient to find out if he had any amino acid defect which could weaken his collagen, but found none and thus assumed his collagen was normal. The defect may lie in its web patterning.

We could not correct his problem by surgery or by truss, as in the case of abdominal hernias. Shoes with a tight heel gave no help. We found, as our patient had, that avoidance of long periods of standing was the only obvious and conservative treatment. Fortunately, his college education should enable him to find a painless job with his feet up on a desk!

QUESTIONS FOR THE DOCTOR:

- Is your patient wearing shoes that are too small?
- Do x-rays of the feet reveal any bone spurs?
- Does the patient have arthritis?
- Does the patient have collapsing arches?
- Could the patient have plantar fasciitis, sometimes triggered by hidden infection elsewhere?
- Does the patient have pain in his feet when lying down or only when standing?
- Have you examined the sides of the patient's feet when he stands up, searching for soft tissue lumps that are painful when squeezed, and when he lies down?
- Does the patient have poor circulation?
- Do the patient's legs swell up with prolonged standing?
- Have you done a skin biopsy of a lump visible when the patient stands up?

26

HOT FLASHES AND COLD CREAM

"I've been having hot flashes for three years and no one knows why," stated a thirty-one-year-old secretary. It soon developed that not only did she get sudden flushes, but they were accompanied by both hives and headaches during severe attacks. She had noted that both the flushing and hives began about an hour after arising, and continued to develop throughout the day and evening, vanishing while she slept. The flushing then began again the next morning as a gradual wave of warmth spreading over her head, neck, and shoulders. The hives were small and scattered over the trunk.

Complete gynecologic and endocrinologic workups were to no avail. She was taking no medications and denied chemical exposures at work. Furthermore, the flushing, hives and headaches did not remit during vacations. It was not occupational.

Examination at her first visit found our patient to be healthy, but her face, neck and shoulders were flushed and warm. There were isolated small wheals, less than a half inch in diameter, scattered over these areas as well as her trunk. Individual hives faded in one to two hours, even as new ones developed. Firm stroking of her skin produced a linear hive, the cardinal sign of dermographism, a condition known as "skin writing." More importantly, it told us that the cause was something circulating in her blood. It could be a food or something she was inhaling.

After seemingly endless questions concerning all her exposures, from douches to dusting powders and cough drops to chewing gum, we focused on just one: peppermint. She told us how she awakened each morning to brush her teeth with a peppermint toothpaste. Then throughout the

day she consumed peppermint life-savers. Furthermore, for the past seven years she had smoked mentholated cigarettes, a pack a day. Knowing that menthol is the essential aromatic ingredient of peppermint, our diagnostic nostrils dilated. Could it be that the toothpaste, life-savers and cigarettes were the cause of her three years of hives and flushes? We asked her to completely avoid all three. She could use Craig Martin Toothpaste which has no flavoring, even as she switched to mint-free life-savers and regular cigarettes.

The success was remarkable and complete. We then documented her specific allergy to menthol, the peppermint compound. This was done by giving her a trace amount of menthol dissolved in alcohol by mouth. After thirty minutes she was flushing. By forty minutes she had a pounding headache. Blood samples drawn at this time showed that her basophils had undergone allergic degranulation. Even a patch test to menthol on the skin produced a fiery red reaction in three minutes. In control subjects, such menthol challenges were without effect.

But our confidence was soon shaken. After weeks of "cure" by simply avoiding peppermint and its active ingredient, menthol, our patient had another attack of hives just before retiring. Again, we combed her history. She rewarded us by saying, "Yes, I remember that night we had roast beef for dinner and I had a big serving of mint jelly."

Two later attacks, each in the evening, demanded the same detailed quizzing. In both instances her flushing followed formal parties, in which she had used lots of makeup. No, it was not the makeup. It was the Noxzema® facial cold cream used to remove her makeup, which contained menthol, famous for its cooling effect.

Now, a year later, there has not been a single attack. The moral: It is not enough to know the precise chemical causing an allergy. You must know and avoid every single thing that contains it.

QUESTIONS FOR THE DOCTOR:

- Does embarrassment cause your patient to flush?
- Does drinking alcohol (particularly beer, sherry, red wine) induce flushing?

- Does tooth brushing with mint-flavored toothpaste induce flushing?
- Is your patient taking any medications that might cause flushing, such as nicotinic acid, isoniazid, indomethacin, griseofulvin, metronidazole, cephalosporin, or a calcium channel blocker (diltiazem, nifedipine)?
- Does the patient eat a lot of cheese, mushrooms, chocolate, or other foods that might induce flushing?
- Does your patient frequently eat histamine-rich foods, including salami, tomatoes, spinach, chicken, or blue cheese?
- Does the patient get flushing from food additives, such as nitrites (bacon), sulfites (lettuce), or monosodium glutamate (Chinese food)?
- Do thermally hot foods make your patient flush?
- Do hot spicy foods containing chili peppers induce flushing?
- Is your patient having hot flashes due to menopause?
- Does your patient take tamoxifen?
- Has your patient had a gastrectomy, which could be causing the dumping syndrome with tachycardia, sweating, dizziness and weakness?
- Have you ruled out possible pheochromocytoma by checking plasma catecholamines during an attack and twenty-four-hour urinary metanephrines?
- Does your patient frequently ingest peppermints or mint jelly, drink mint juleps or mint flavored tea, or apply mentholated creams?
- Does your patient use recreational drugs, such as morphine, amyl nitrite, or butyl nitrite?
- Does your patient have hypertension during a flushing attack?
- Have you checked urinary histamine for an indication of mast cell degranulation and histamine release?
- Have you checked for carcinoid syndrome by obtaining a twenty-four-hour urine specimen for the serotonin metabolite, 5-hydroxyindolacetic acid (5-HIAA)?

27

THE BLISTER AND THE SKIN TEST

A fifty-two-year-old housewife knew her diagnosis. It was erythema multiforme. But "why," she asked, "does it keep coming back?" It all started seven years ago when she was vacationing on an island off the coast of Mexico. She had numerous blisters, diagnosed as a reaction to insect bites. They slowly faded over the next month, only to reappear six months later, when her mouth also became ulcerated. This time it took two months for healing. A third attack was attributed to eating too much chocolate. Subsequent attacks were erratic, but in the last year there had been six distinct episodes.

Her close observation of these attacks taught her that each one was preceded by a cold sore on her lip, face, or nose. Invariably, seven to ten days later she would see her skin covered with small and large blisters. They were strangely floral in their patterns, with rings of purple giving them a target or iris look. Dermatologists had made the diagnosis of erythema multiforme, of the blistering (bullous) form.

But the diagnosis did not tell her, or any of her doctors, about the cause of her blisters, or suggest how she could avoid these disabling attacks. Erythema multiforme was only a name, used to describe the way the skin reacts to at least seventy different causes. What she had was a reaction pattern, but to what was she reacting? Could it be a drug? No, she had no common thread of any particular medication before each attack. Could it be a reaction to a tropical plant, or even poison ivy? No, she had had no further exposure to these. Could it be a sign of malignancy, a lymphoma, or lupus? Could it be a food allergy? Although chocolate has been a reported cause, strict avoidance of chocolate gave her no protection. All of her tests were negative.

Could it be due to an infection? Here we had to say yes, possibly. Her cold sores were an infection with the herpes simplex virus, and other patients had noted that such an infection at times preceded their attacks of erythema multiforme. But how could a simple cold sore set off such an explosive widespread blistering?

Over a period of a year we studied our patient closely. Skin testing to over twenty bacterial and fungal antigens was negative. X-rays of the chest, gut, and sinuses were normal, as were repeated health profiles of blood and urine. But we lacked a skin test to the herpes simplex virus, for which we had been waiting seventeen years to test the hypothesis that a cold sore could cause erythema multiforme. Even as we were studying this patient, however, the pharmaceutical firm, Eli Lilly, was preparing an experimental vaccine from the Herpes simplex virus to see if it could prevent cold sores. It did not, but the vaccine extract allowed us to prove that the cold sore virus could cause erythema multiforme in patients.

An injection of the Lilly herpes cold sore antigen into her skin produced a large local target design blister after forty-eight hours. Furthermore, new blisters cropped up on her body. We had reproduced the disease. We had shown the cause. All the proper controls on fifteen other patients, as well as tests with the nonviral components of the vaccine, were negative.

Drugs and cancer can still be other specific causes of the erythema multiforme reaction pattern. We got negative skin tests for herpes allergy in patients who had erythema multiforme associated with sulfa allergy and cancer of the bowel, respectively.

With the advent of new antiviral therapy for herpes simplex, our patient was cured. No more cold sores meant no more erythema multiforme. And the woman, Gertrude Elion, who discovered the drug, Zovirax® (acyclovir), was awarded the Nobel Prize for it. We know our patient would have gladly made the presentation.

QUESTIONS FOR THE DOCTOR:

- Do her blisters get worse before her period?
- Does she have any evidence of insect bites?

- Do some of the blisters resemble targets?
- Does she suffer from recurrent cold sores?
- Is she taking any of the 250 medications known to produce erythema multiforme (e.g., penicillin, sulfonamide, or botulinum)?
- Has a long-term trial of oral acyclovir prevented further attacks of blisters?
- Do any specific foods, such as chocolate or nuts, bring out the blisters?
- Have you done a skin biopsy, with immunofluorescence, to confirm a diagnosis?

28

A CHILLING PAIN

Chilling the skin of this five-year-old boy was like sticking a dagger into him. Contact with any cold object brought him unbearable pain. Even a moderately cool drink would make him vomit. It had been that way ever since birth, his parents told us. Our patient treated a cold object as the rest of us would treat an open flame. There was no family history of such a condition.

On examination this little boy was a happy healthy individual with perfectly normal skin. But when he was held down, his trust betrayed, to test his skin reaction to a tiny ice chip, he became a pathetic screaming child covered with tears and muscle spasms. The test site with the ice chip flared out four inches with bright red skin and local sweating. The edges of the erythema were irregular, as seen with blood vessel dilatation induced by local nerve paths. There was no hive. The redness and screaming remained for a full hour. Later, the skin was perfectly normal again.

Testing with tubes of water at varying temperatures showed that his reaction developed whenever the temperature was below 68°F. Hot water was tolerated normally, but being put in a cool room was tragic torture. His skin sensory system seemed normal with touch and pain responses being unremarkable.

We had never seen such a reaction to cold. As we reviewed our experience with cold as a cause of disease we remembered that we had seen hives develop in chilled skin. This was due to histamine released by the chilled mast cells in such patients. We had also seen dark bluish discoloration of the fingers and toes from infections that produced cold agglutinins. These proteins thickened in the cold, resulting in blood vessels being plugged

by clumped (agglutinated) red blood cells. Finally, we had seen similar purpura in patients with lymphoma, whose blood also contained a protein which precipitated when the skin and vessels were chilled. But our patient proved to have none of the above in his blood.

A skin biopsy showed perfectly normal structure. We were able to reproduce the redness by injecting either his own blood after it had been chilled and then rewarmed or a chemical nerve messenger, called serotonin. We had no way of determining his pain response, because he screamed throughout all of the tests.

Therapeutic trials with a variety of drugs did not help, but the sovereign cure came when the family moved to warm sunny California, where he now leads a happy pain-free life. We are sure he still has to tell strangers, "Don't ever give me a cold drink. I am allergic to cold."

This was a puzzling congenital problem in which cold released some chemical that in him, and him alone, set off protective reflexes. At the time, our best lead was that this agent was serotonin. Today, we would suspect Substance P, a pain substance not known at that time. Whatever the cause, this little boy remains as vivid in our memory as another little boy who was brought to us because he could not feel pain. Both had to make serious adjustments to their environment and both were to be pitied.

We named this new disease cryodynia.

QUESTIONS FOR THE DOCTOR:

- Was the patient born with cold sensitivity?
- Have you tested for cryoglobulins, cryofibrinogen, and cold agglutinins in the blood?
- Have you measured serum histamine, serotonin, and substance P during an attack?
- Have you searched for hidden infection, such as mycoplasma, in your patient with cold sensitivity?
- Have you given your patient a trial of oral antibiotics, such as minocycline or clarithromycin?
- Have you done an ice cube test, holding it on the skin for two minutes?
- Has the patient tried moving to a warmer climate?

29

ROUGH SKIN AND SORE THROATS

"I've tried a dozen creams and lotions on him but nothing helps" was the plaintiff comment of the mother of an eight-year-old boy. The boy's upper arms were as rough as sandpaper, studded with numerous tiny plugs of keratin, the protective outer skin protein. On skin biopsy they were seen as compact plugs filling the hair pores, with no inflammation. Most of the doctors had dismissed it as trivial and insignificant, hardly worthy of a prescription. Actually, they did not know of an effective remedy, prescription or otherwise. Here was another orphan patient, not because his disease was rare, but because it was so common as to be accepted as a mundane non-disease.

Rough skin due to dry keratotic material in the upper hair follicles can be the presenting complaint of at least ten dermatologic disorders. We ruled out the rough skin colleague, keratosis follicularis (Darier's disease), by both biopsy and its localization. Another diagnostic possibility, pityriasis rubra pilaris, was similarly discarded, for this rare disease is, as its name indicates, red and scaly. Since the lesions had no spines in the hair follicles, lichen spinulosus was dropped from consideration. To continue the polysyllabic diagnostic litany, he did not have keratosis pilaris decalvans or keratosis pilaris atrophicans, for there was no hair loss or scarring. It was also not the Vitamin A deficiency of phrynoderma, seen in the malnourished. Neither did he have any signs of fish skin-like scales, as in ichthyosis, which may produce horny plugs, nor was there any evidence of atopic dermatitis with its terrible itch. No, this was plain old-fashioned, commonplace keratosis pilaris.

A careful physical examination, as well as an in-depth history, pointed to one possible cause. This boy had greatly enlarged tonsils and had a history of frequent streptococcal sore throats. We suspected that this same class of bacteria, which causes scarlet fever with its red skin and sandpaper-like rough skin, might be responsible.

Accordingly, we prescribed the antibiotic, erythromycin, to be taken both as a treatment for his current "raw" sore throat, but also as a long-term prophylactic. The results were gratifying. Within weeks his skin became smooth, and his throat was no longer susceptible to the streptococcal toxins. If erythromycin had failed to help, we would have recommended trial periods of other antibiotics, such as penicillins, clarithromycin, or cephalosporins.

We left him on the antibiotic throughout the winter. He has remained safe from sore throats and rough skin. His mother was pleased that her orphan patient had found a "home" and we were pleased to have found a treatment for keratosis pilaris by doing some lateral thinking, stimulated by a rheumatologist who told us his son developed rough skin whenever he had a sore throat.

QUESTIONS FOR THE DOCTOR:

- Does your patient have extremely dry skin, requiring frequent use of moisturizers?
- Does your patient take frequent baths or showers, which could contribute to dry skin?
- Does your patient have to cut back on bathing in the winter due to itching?
- Does your patient get enough vitamin A in his diet?
- Could your patient have an inherited form of ichthyosis?
- Does your patient suffer from recurrent sore throats, earaches, or sinus infections?
- Does your patient's skin improve during treatment with antibiotics for underlying infection?

30

THE PREMENSTRUAL PURPLE CHIN

The mother gave the history that for three years now her teenage daughter had been developing a purplish discoloration of her chin approximately three to five times a year. But now, the episodes were occurring with increasing frequency. The purple chin had appeared just prior to her last three menses. The attacks always came during school hours, and the color gradually faded during the following week. The skin always returned completely to normal.

We turned to the girl. What could she tell us? She described her chin as suddenly turning purple and becoming tender and painful. Her lips became swollen at the same time. Later, her chin was itchy. Steroid therapy, both orally and locally, had given no help. The attacks continued to come.

The daughter was a healthy thirteen year old. All of her blood tests were normal, and when we examined her nothing could be seen on the chin. We asked her to return during her next attack. Three weeks later, just before her menses, her chin suddenly became purple. We saw her five hours later, noting her chin to be diffusely discolored with a light purple color along with some dilated small blood vessels.

The premenstrual flare led us to believe she had a sensitivity to her own female hormones. We knew that progesterone, made by the ovary, reached its highest blood levels just before the menses. And we knew that some patients become sensitive to their own progesterone, resulting in "progesterone dermatitis" manifest as acne, hives, or eczema. But we had never seen a progesterone purple chin.

We secured a skin biopsy which showed many dilated capillaries, but no obvious skin disease. Blood assays showed that all of her hormone

levels, including estrogens, were normal. Intradermal skin tests with sixteen hormones, including progesterone, were negative. We recommended that she take tamoxifen, a drug which blocks the actions of female hormones. But it totally failed to prevent the next attack.

We continued to be puzzled, but on the fourth visit we saw that her most recent purple chin had sharply outlined borders. We then realized that her sudden attacks in school were the result of suction. She evidently held a cup or glass over her mouth and chin, and with deep sucking produced dilated blood vessels and slight bleeding into the skin, known as purpura. Had she done greater damage, she would have had a "black and blue chin."

Close questioning now revealed that the patient was unhappy about her general appearance and also being overweight. Her school performance was mediocre, and she was having trouble dealing with the general turbulence of being a teenager.

We gave the mother insight into the nature of her daughter's mysterious purple chin and the fact that it was a plea for attention. And as for the daughter, she always knew how the problem came about.

QUESTIONS FOR THE DOCTOR:

- Does your patient seem to be unhappy?
- Have you taken a careful history about her home, school, and social life?
- Did you detect a pattern in the development of your patient's skin lesions?
- Could your patient's skin lesions be self-induced (factitial)?
- Is there a peculiar sharp margin to your patient's lesions, unlike those usually produced by "Mother Nature"?
- Have you prescribed an anti-depressant or psychotherapy for your patient?
- Have you taken a photograph of your patient's lesions for future reference/comparison?

31

NINE YEAR HIVES

"What can you do for my hives?" It would seem that there was nothing more that could be done for this twenty-seven-year-old woman's hives. She already had been carefully studied and treated by a succession of doctors, including an allergist, an internist, and a dermatologist. She had even been hospitalized twice. No cause had ever been found and the hives could be controlled only with steroids.

The attacks had begun six years ago. At first they were only occasional visitors, but soon they developed into severe generalized hives which came every day. For the past three years, whenever she scratched her skin, a hive came up.

The salient features in her hive history were: 1) onset after an automobile accident; 2) anaphylactic shock after injection of the drug, ACTH, suggestive of an allergy to pork; 3) no family history of hives; 4) no association of the hives with either the menses or taking aspirin; 5) usually worse in the morning hours.

Thus began a three-year odyssey of study, tests, and therapeutic trials. Routine blood studies, as well as tests for lupus, were repeatedly normal, as were x-rays of her chest and teeth. There were no dental abscesses evident. Biopsy of the skin showed only the local accumulation of fluid, typical of urticaria.

The absence of basophils from her blood, and the presence of dermographism (skin writing) indicated to us that at all times she carried the antigen responsible for her hives. But what was it? Scratch tests to some twenty molds and bacterial antigens were negative, except for staphylococcus. Twenty intradermal skin tests to foods did show hive

reactions to beef and to rye. Stool examinations revealed no ova or parasites.

Over a three-year period we made many therapeutic trials, but the only drugs that helped were antihistamines and cortisone, which suppressed the hives but did not cure them. We wanted to find their cause, and by eliminating it, eliminate her hives. We prescribed a series of medications to eliminate yeast infections, bacterial infections, and parasitic infections. None helped. By actual count we had tried short courses with eighteen of them.

We next tried eliminating all drugs, cosmetics, toothpastes, perfumes, and sprays, any one of which could be causing her hives. But, again, no success. We tried food elimination diets. We had her undergo a tonsillectomy. During this period she also tried formal psychotherapy. But still the hives continued every day.

Finally, we had her enter the hospital for the third time, with two objectives in mind: conduct more radiologic studies to search for a hidden tumor or abscess; and isolate her from all foods, drinks, and inhalants. Within two days on a *no food* diet her hives were all gone. We were delighted and proceeded to have her start back eating with the most hypoallergenic food we knew, namely chicken. Back came the hives that very day. Amazing we thought, but let's wait until they go away and then add apples. Back came the hives.

We suddenly wondered if the simple act of chewing could somehow be the cause of her hives. Yes, it *was* chewing. The hives came out from simply chewing on a paraffin wax! We then suspected she had an occult dental abscess, even though she had had no toothaches and many sets of dental x-rays had all been normal. We now knew that for her, to chew was to hive.

We sent her back to the dentist with instructions to please look for an abscess the old-fashioned way, with a probe. With this probe he found a pocket of pus that shot out from beside the third molar. This pus had been radiolucent, not seen on x-ray. Her hives then became much worse, and even after extraction of the tooth she had no relief.

So, she returned to the dentist, and to his continuing amazement, he found another molar submerged in pus. Within a week of its extraction our patient was truly hive-free for the first time in nine years. No hives ever returned after the steroids were stopped, a full diet was resumed, and the doctor visits were terminated. Finally, we could understand why her hives had always been worse in the morning. It was then that she

brushed her teeth, pushing the bacteria and pus, along with their antigens, into her blood stream and hence to the skin, releasing histamine from her mast cells. Her allergy was remarkably specific; as subsequently when she developed a cystitis (bladder infection) and later boils, no hives returned.

The low success rate in solving the riddles of chronic hives is underscored by a Mayo Clinic report in which 70% of their cases never had any cause found. In only 7% could a specific cause be discovered, although 23% were labeled psychogenic. Yet, a report in the dental literature reviews 100 patients with chronic urticaria, in whom six were cured by dental treatment. Not only focal dental infection can cause hives, but also the materials dentists implant, such as penicillin, clove oil, and metal amalgams. The teeth deserve a careful review in all cases of chronic hives.

The value of close study in the hospital is underscored by our success in finding true food allergies by this means. One was potato, another was sage. But not all hive patients need hospitalization. We recall some of our lucky single visit cures of chronic hives. In one, the cause was evident by simply looking at her feet. She had athlete's foot, and curing this with griseofulvin cured her hives of many years.

Another woman who came with hives was cured by our prescription for treatment of her underlying vaginal yeast infection. In fact, eliminating yeast infection cleared about 30% of women with chronic hives in our practice. A third reminder of "first visit" cures was a doctor's son who knew he was allergic to penicillin, but avoiding penicillin had been of no help. We cured him by taking milk out of his diet, because we knew that at that time milk often contained traces of penicillin given to treat cattle.

We don't accept hives. We accept only the challenge of finding the cause of the hives.

QUESTIONS FOR THE DOCTOR:

- Has your patient tried an elimination diet for two weeks, completely avoiding milk, cheese, pork, eggs, nuts, corn, and fish?
- Has your patient stopped all oral medications for two weeks, including drugs, vitamins, and herbals?

- Does your patient chew mint-flavored gum, consume peppermint or wintergreen lifesavers, or smoke mentholated cigarettes?
- Has your patient had a dental consultation that involved searching for hidden abscesses?
- Have you treated your patient for possible hidden vaginal yeast infection?
- Has your patient been checked for intestinal parasites?
- Has your patient traveled to foreign lands?
- Has your patient stopped using all cosmetics, perfumes, shampoos, and toothpaste?
- Is there a daily, weekly, or monthly pattern to your patient's hives?
- Is your patient exposed to inhalants at work?
- Is your patient exposed to incense or other aroma therapies?

32

GOLF COURSE DERMATITIS

When a fifty-one-year-old man first walked into our office that August afternoon, covered from head to foot with a rash, we knew he needed to be hospitalized. But he refused. "It'll go away, Doc, next month." So, as our nurse gave him an emergency injection of steroids, we sat down to listen to his intriguing story.

It had all begun five summers before as a hand eczema. He associated the problem with taking up a new sport: golf. He was an automotive repair specialist who had never been bothered by any of the sprays or paints with which he came in contact. Steroid creams had helped, but his hands never really cleared until golf season was over.

Each subsequent summer the eruption reappeared when he resumed golf. And each summer it had become worse, eventually involving his wrists, arms, legs, neck, and face. Last winter, for the first time, involution did not come and his hands never cleared. Again, this summer he was having to go to doctors for steroid injections. But, play golf he would.

We could certainly agree that he had golf course dermatitis. But why? We struggled to bring out more history. He observed that his right hand, used to pick up the golf ball, was always the worst. And then came his seminal observation that the worst flare ever came explosively the day after he walked by some men spraying the greens.

The race was on. What was in the spray? It proved to contain thiram, a powerful fungicide chemical, used to keep the golf greens healthy and green. Patch testing with the thiram powder, in contact with his skin for only fifteen minutes, produced a strong eczematous reaction thirty hours later, coupled with a flare-up of all of his rash.

He truly had a golf course dermatitis due to his unique sensitivity to thiram. At that time this compound was widely used in disinfectants, larvacides, fungicides, rubber goods and, most importantly for him, as a bactericide in Lifebuoy Soap. Our study proved that he was washing that dermatitis right into his skin!

Fortunately, he was not a drinker of alcohol, since the other effect of thiram is to sensitize individuals to alcohol. Interestingly, the drug, Antabuse®, is a derivative of thiram. A dose of this drug followed by a drink of alcohol may make a person so toxic he never wants to drink again. It is not an allergic reaction limited to a few, as in our patient's eczema, but a phenomenon for all.

One of our other patients came to us saying he was allergic to alcohol. Could we do something? He simply could not tolerate an alcoholic drink, which made him violently ill. And it also made him sick to be deprived of his cocktails. We had previously seen patients whose skin was allergic to alcohol, which caused a rash, but this was different. On questioning we found that this man lived by a golf course where the fungicide, thiram, was frequently sprayed. This spray had made him sensitive, but not allergic, to the cocktail he was drinking on his patio as the sprayers went by. He is still grateful to us for bringing back his booze! All he had to do was stay indoors and keep his windows shut when the sprayers were nearby.

With modern chemical industries introducing chemical antigens into thousands of products, the unfortunate victim of sensitization has few places to hide and few products he can trust. Witness the arsenic now found in wallpaper, weed exterminators, cotton garments, woolens, raw furs, and bronze powder.

Our poor patient had to fear not only the golf course, but also his soap, rubber goods, germicides, and even sunscreen preparations of that time. For him, living in our man-made environment is more hazardous than walking among poison ivy plants in the natural environment.

QUESTIONS FOR THE DOCTOR:

- What does your patient think is causing his rash?
- When did the rash first start?

- Is the rash related to sun exposure?
- Is anybody else around the patient itching?
- Is your patient taking any medications that might induce photosensitivity, such as thiazide diuretics?
- Does your patient drink alcohol?
- Does your patient have seasonal pollen allergies, such as hay fever due to grass or ragweed?
- Does your patient keep tropical fish, so that he might be allergic to midges in the fish food?
- Does your patient have pet birds or rabbits, which might expose him to "bite and run" mites?
- Does your patient have indoor cats or dogs, which could expose him to fleas, mites, or animal dander?
- Has your patient been exposed to any weed or insecticide sprays outdoors or at home or work?
- Does your patient use hair spray, aftershave lotion, spray deodorant, or other fragrance? How about his wife?
- Have you taken a detailed history of your patient's hobbies?
- Have you taken a detailed history of all of your patient's medications, including prescriptions, vitamins, herbals, and salves?
- Have you examined your patient's teeth and throat for possible hidden infection?
- Does your patient have tinea pedis, unguium or cruris, which might be causing a disseminated fungal "id" reaction?
- Could your patient have candidiasis?
- Does your patient have a history of cold sores?
- Has your patient had any venereal diseases?

33

THE SECRET MESSAGE

"It's her hair," the mother said as she brought in her fourteen-year-old daughter. What we saw were two stripes of bald skin running across the girl's scalp. Present for two years, they crossed forming a perfect crucifix pattern. It looked as if one had run a hair clipper from the forehead posteriorly to the nape of the neck, and then clipped a 3/4 inch band transversely to form a precise cross. The margins were straight as an arrow, so geometric that we realized it was nothing nature could produce. It had to be the patient.

She was pulling her hair out. It was not the total loss of alopecia areata with its round patterns of totally bald skin. A pluck test showed that her hairs had excellent root strength, and a twist test proved the hairs were not fragile and could not be broken easily. The very short stubble present in the bare areas suggested to us that she would pull the hairs out as soon as they were long enough to grasp with her fingers. Her skin was perfectly normal, and the other doctors she had seen for this problem had found her to be in excellent health on physical and laboratory examinations.

We made the diagnosis of trichotillomania, i.e., hair loss due to the patient pulling out her own hair. It was a nonverbal cry for help. We usually see it in children brought in with the complaint of thinning hair. Sometimes the mother finds a clump of hair on the child's pillow. Occasionally, the child actually eats the hair, and a hair ball (trichobezoar) is found in the stool, explaining the hair loss as well as the accompanying stomach aches. But this patient had the most dramatic pattern of hair loss we had ever seen. She was sending her parents a secret message. But, what was it?

It takes time to decode this form of hair loss. One cannot ask directly about an underlying emotional problem. Indeed, few parents will accept the diagnosis of trichotillomania. We usually indirectly hint that the hair loss may have something to do with stress. Still, there is often denial and rejection of this concept by the parent. One of our close friends brought his nine-year-old daughter in with thinning hair. When we suggested to him that she might be pulling it out because he kept pushing his daughter to get all A's in school, he walked out of the examining room and never spoke to us again!

While we waited for an answer to the meaning of the cross, we simply told the girl her hair was very loose and she must not ever touch it. She must wear a cap on her head at night so she would not accidentally pull on any hairs. We also asked her to take biotin, three tablets a day, since this vitamin promotes new hair growth. We also predicted that in three weeks, when we planned to see her again, she should have lots of nice new hair growing in those bald strips. That was our secret message to the patient. She knew that we knew what she was doing.

We never told the mother that her daughter was pulling her hair out, but instructed her to do everything possible to relieve her daughter's stress, such as pamper her, baby her, and love her.

They came back in three weeks, both happy. Hair was growing in beautifully and the mother had gotten the secret message: *No sacrament of confirmation.* As they left, we could see a cross being lifted from both the daughter and the mother.

QUESTIONS FOR THE DOCTOR:

- Did you interview the patient alone, without her mother being present?
- Did you confront the patient and ask her why she is pulling her hair out?
- Did you do a skin biopsy to confirm the diagnosis of "traction" alopecia?
- Did you refrain from sharing her secret with her parents?

- Did you take a thorough social history from the patient and her mother, including problems at school?
- Did the mother find hair in her child's bed?
- Did you examine some "lost" hairs under the microscope for evidence of trauma to the hair shaft and bulb?

34

HERPES GLADIATORUM

An eighteen-year-old college wrestler was admitted directly to the hospital. For five days he had suffered widespread blisters of his forearm, neck, forehead and scalp, which were now oozing and crusted. We counted over fifty such plaques. On the day of admission his right knee had become markedly tender, hot, and swollen.

He gave a past history of having had shingles when he was four years old, a severely wrenched right knee at age eleven, and an allergy to sulfa drugs. He had never had fever blisters or cold sores.

We knew what his skin problem was. It was the result of the fever blister virus (*Herpes simplex*) being rubbed into each of those fifty areas. One of his fellow wrestlers must have had an active cold sore which contaminated the wrestling mat. Since this was his first contact with the virus, every site touched by the virus developed a cold sore. He essentially had fifty fever blisters simultaneously. He would not have developed a single one if only he had had a prior fever blister on his lip, due to immunity to the virus. Only his own virally-infected nerves would then set off periodic flares of a cold sore, always in the same location.

Yes, we knew his skin story well. He had herpes gladiatorum, an occupational disease of wrestlers. We later learned that two of the men he wrestled with also came down with the same problem. But, the real mystery was still the swelling in his right knee.

A skin biopsy contained the diagnostic swollen giant cells seen in herpes simplex, but there was no evidence of the herpesvirus in a synovial biopsy from his right knee. Type I herpes simplex virus was cultured from a blister of the right arm.

Routine blood studies were normal, as were the serologic test for syphilis and liver enzyme levels. Chest x-ray and studies for lymphoma were likewise normal.

The mystery of the swollen right knee was solved when we got the culture report on the effusion fluid. It contained the same Type I herpesvirus, but no bacteria. He thus had herpetic synovitis.

Now we could see the importance of a good history. The herpesvirus in the skin had entered the blood stream, causing a viremia normally contained within the blood vessels. But because of the traumatic injury to his right knee seven years ago, the virus was able to enter the right knee and set up infection. Meanwhile, the uninjured left knee remained normal.

This was a most instructive patient, as he taught us that the body never forgets. Although his right knee had healed after the twisting seven years ago, microscopically it remained weakened, enabling leakage of virus into the joint. He was the first person known to have had arthritis confirmed to be due to a viral infection.

We suspect that the localization of skin lesions, from psoriasis to eczema, commonly reflects local injury sites going back many years. Perhaps, the long forgotten chickenpox of yesteryear might even determine where the "sun spots" of today come out. The Romans had a phrase for it: *"Locus minoris resistentiae."*

QUESTIONS FOR THE DOCTOR:

- Has your patient ever had cold sores or been exposed to them within the family?
- Has your patient been in close contact with anyone with sores, impetigo, or cold sores?
- Is your patient a wrestler?
- Is your patient sexually active?
- Did you explain to your patient that herpes simplex lesions always recur in the same spot?
- Did you take a careful history of previous injuries, which could serve as points of localization for future lesions (i.e., skin memory)?

- Did you do bacterial and viral cultures of the skin and joint lesions?
- Did you give the patient a trial of oral acyclovir for his skin and joints?
- Did you do a skin biopsy?
- Did you do a Gram stain and Tzanck smear on a scraping of the blister base?

35

SUNSHINE ALLERGY

"I am allergic to sunshine" was the complaint of a fifty-nine-year-old man. "And, I have been so for seven years." Allergy is a wonderfully creative word. Allergy, virus infection, and nerves are used to explain nearly all of a patient's inexplicable problems. Allergy, especially, has many definitions. We recall having offered to buy ice cream cones for two little girls. The older one said, "But my sister can't have chocolate. She's allergic to chocolate." Really? "Yes, she smears it all over her dress and it stains."

So, the question was, what was his allergy? We learned that the exposed areas of his forearms, ears, and forehead would become bright red and even blister after just five minutes of direct exposure to sunlight. Later, the areas itched fiercely for a day or two, and then the skin returned to normal. This allergy had kept him indoors for those seven years.

His prior history revealed a gastrectomy thirteen years ago with two-thirds of his stomach having been removed. He took no medicines, used only Ivory Soap for cleansing, and applied no hair sprays, colognes or after shave lotions. Alcohol intake was limited to an occasional beer. There had been no diarrhea or mental disturbance. He slept poorly, however, and said he always felt nervous.

His skin appeared normal, but phototesting with direct sunlight in July revealed a minimal erythema dose of five minutes (the minimum exposure time to give redness). Upping the dose of sunlight to twenty minutes resulted in a red bumpy (papular) rash that persisted for three days. It was possible to block this reaction with a sunscreen. A skin biopsy of this reaction showed only mild inflammation, with no sign of lupus

erythematosus. Laboratory studies for lupus, as well as the photosensitizing porphyrins, were normal.

The usual causes of sunlight sensitivity are drug allergy, as to a sulfonamide diuretic, or a reaction to a chemical applied to the skin, such as a perfume. Another cause is liver disease, sometimes linked to the hepatitis C virus, which results in increased amounts of porphyrins in the blood, urine, and stool. In the absence of such leads we followed the patient's health trail, which dead-ended with his poor diet and gastrectomy. We wondered if he could have a subclinical form of pellagra with his poor diet and long-ago gastrectomy causing nicotinic acid deficiency. We knew that at one time pellagra was a common disorder, affecting millions of people who ate mainly corn. It was characterized by the "***three D's***": ***d***ermatitis from sunlight, ***d***iarrhea, and ***d***ementia. The discovery that nicotinic acid as a dietary supplement cured this disease literally established the scientific field of nutrition. Could our patient perhaps have just one leg of the three-legged stool of pellagra? We would see.

We "prescribed" over-the-counter nicotinic acid 100 mg twice a day. The results were phenomenal. On the tenth day, exposure to two hours of sunlight produced no reaction! Since then he has continued to take nicotinic acid daily and live a normal outdoor life.

"Allergy" comes in many forms. In this case it was nutritional.

QUESTIONS FOR THE DOCTOR:

- Is your patient taking any photosensitizing medications?
- Does your patient have a poor diet that could be deficient in vitamins?
- Has your patient had a gastrectomy that could lead to a nutritional deficiency?
- Does your patient have diarrhea or any signs of dementia?
- Have you given your patient a trial of nicotinic acid?
- Did you do an ANA on your patient?
- Did you give your patient a trial of oral beta-carotene to try to decrease his photosensitivity?
- Have you checked the patient's blood and urine porphyrins?

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L'HOMME ROUGE

A sixty-three-year-old man came to us with his entire skin fiery red and tender. And, it had been that way for over a year. He had what is known as chronic erythroderma or exfoliative dermatitis, (French: *l'homme rouge*). He had lost most of his hair and fifty pounds of weight.

The mystery was the cause, not the diagnosis. Erythroderma has many causes. We could eliminate the two most common ones, longstanding eczema and psoriasis, because he had never had any skin disease before.

We ruled out a malignant lymphoma by skin biopsy, and also eliminated internal tumors by x-rays and CT scans. But the cause of his total body rash still eluded us, although we had clues it was due to an allergy. His complete blood count (CBC) showed an eosinophilia of 36%, which meant that a large number of his white cells were eosin staining, a certain sign of allergy (in contrast to the normal 0% to 5%). Furthermore, a second skin biopsy suggested that drug allergy might be the cause. However, he was taking no medications by mouth, and had only occasional cortisone injections to calm down his redness, itch and scaling.

Yet, there was one more item of medication to be considered, his eyedrops. They seemed so innocent and insignificant, used to control his glaucoma. We were, of course, reluctant to eliminate them, fearing progressive blindness. But until we finally stopped them, we could not control the eczema which covered every square inch of his body. Within a month of discontinuing the eyedrops, his erythroderma was better with less itch and some regrowth of hair.

Amazingly, his timoptic eyedrops were the cause of his two years of misery. But now, his glaucoma worsened and another beta-blocker eyedrop

was prescribed. The erythroderma flared again. Only by using a completely unrelated eyedrop containing pilocarpine were we able to save his eyes, as well as his skin. After seven months away from the timoptic eyedrops, his dermatitis was virtually gone, his hair growth was excellent, and he was regaining some weight.

The eyedrop always sounds too safe to be suspected as a cause of disease. After all, it causes no apparent trouble in the eye, or the ophthalmologist would stop it. Yet, it can be absorbed and cause harm far away from the eye, such as the fierce generalized itch that no one understands. Eyedrops can also slow the heart, lower the blood pressure, lead to heart failure, and interfere with breathing – not because of allergy, but due to blocking of nerve impulses anywhere in the body their chemicals are carried by the blood. In some patients eyedrops set off manic depressive attacks, while other patients have reported hallucinations, confusion, and insomnia. Many elderly people have their eyedrops to blame for their troubles, not their age.

Look to eyedrops as a cause of more than just a simple contact dermatitis of the eyelids. We are glad we finally did in this patient.

QUESTIONS FOR THE DOCTOR:

- Has your patient previously had any skin problems, such as psoriasis, atopic eczema, or contact dermatitis?
- Has your patient ever had a drug eruption?
- Has your patient had one or more skin biopsies to rule out mycosis fungoides?
- Does your patient have chronically dry skin or icthyosis?
- Does your patient work with any chemicals?
- Is your patient exposed to any fumes at home or at work?
- Does your patient have any photosensitivity?
- Does your patient have any hidden infections in his teeth, sinuses, gallbladder, or urinary tract?
- Could your patient have pellagra?
- Have you checked your patient for hypothyroidism?

- Have you done x-rays and a CT scan to rule out internal malignancy?
- What medications does your patient take?
- What topical medications does your patient use for his skin problem?
- Does your patient use eye drops?
- Did you have your patient bring in all of his cosmetics so that you could inspect the ingredients?
- Does your patient have chronic tinea pedis, cruris, or unguium?
- Does the patient have any areas of normal skin where patch tests could be applied?
- Have you done a complete blood count checking for eosinophilia and Sezary cells?
- Have you checked blood chemistries and a urinalysis?

37

RINGS OF RASH

"I've had eight years of rings on my skin and I'm tired of them. The only good news is they only come in the winter," complained a thirty-nine-year-old woman. At first her lesions had been limited to her forearms, but in the ensuing winters the ringed red cords had spread to involve her trunk, arms and legs. They would start out as bumps, then enlarge and clear in the center, leaving mildly itchy red rings that sort of resembled hives. Cortisone would clear them, but they always came back to stay until May.

We knew what she had, but we did not know why. Her diagnosis was erythema annulare centrifugum, which translates into red rings expanding centrifugally while clearing centrally. But what causes it? Again, like so many other skin diseases, it does not have a single cause, but is a reaction pattern to many different things. It can have many patterns, such as polycyclic, arcuate, annular, festooned, serpentine, figurate, geographic, or annular (ring-shaped). Although the shape of the lesions belies the diagnosis, it does not reveal the cause.

Her long-suffering winters led us to admit her to the hospital. We wanted to know for sure that her rings were not a sign of internal malignancy. Fortunately, extensive studies revealed no underlying cancer or any other disease. She had no intestinal parasites found on stool examination, and her tests for lupus erythematosus were negative.

She had given us a history of having had athlete's foot (tinea pedis) as a young woman, but now there was no evidence of this. Yet an intradermal skin test to fungal extract gave a positive reaction with a striking ring shape. Most puzzling, however, was that tests to a dozen other yeast and

mold antigens were negative. We had successfully reproduced her disease with the ringworm fungus, although she had no ringworm infection now. But then she told us that while waiting to enter the hospital she had experienced a sudden flare of "ring spots" immediately after eating a salad with blue cheese dressing. Might the diagnosis have been at the doorstep of the hospital, rather than within it's scientific walls?

We gave her a small wedge of blue cheese to eat. Within thirty minutes all of her skin lesions showed a dramatic flare. Even the twelve previously negative intradermal skin test sites became inflamed, where the blue cheese antigen had leaked out! Within hours new papules had appeared, which later became rings.

Once again, we realized how keeping the allergen (antigen) within the blood stream helps keeps the skin in shape. Recall that scratching the skin can bring out a hive if the patient has an allergen circulating in the blood. This is the basis of dermographism, where a fingernail scratch damages capillaries and allows the allergen to leak out into the skin. Mast cells then release histamine, producing the linear hive of dermographism. Indeed, analysis of the patient's blood at this time showed that all of her basophils had dumped their histamine, just as had the mast cells in her skin wherever the blue cheese antigen could reach them.

It all made sense. She was allergic to the mold in blue cheese. It was a member of the *Penicillium* genus of molds, of which there are several thousand strains. Her sensitivity turned out to be very specific. On subsequent days in the hospital we challenged her with two non-blue cheeses, as well as Rocquefort cheese, whose blue color and flavor comes from *Penicillium rocquefortis*. They had no effect on her skin lesions, but a second challenge with domestic blue cheese produced a second giant flare.

We were seeing the cause of her disease. Even as she was sensitive to the one-time fungus on her feet, now we were seeing a reaction to its relative, the blue cheese mold.

Her cure came not with medicines, but with diet. By avoiding all cheeses, mushrooms, wines, and fruits and vegetables which are prone to be moldy, she has been clear for years. Now the only rings she has are on her fingers.

QUESTIONS FOR THE DOCTOR:

- Is there any pattern to the flare-up of lesions?
- Have you ruled out tinea corporis by doing a KOH preparation and fungal culture?
- Have you examined your patient's feet for hidden athletes' foot and onychomycosis?
- Does your patient have tinea cruris?
- Have you done intradermal tests for possible candida and dermatophyte allergy?
- Did you do a thorough examination to rule out internal malignancy?
- Have you done a stool examination for ova and parasites?
- Is your patient allergic to penicillin or other medicines?
- Does your patient have any food allergies?
- Does your patient drink beer or wine?
- Does your patient frequently eat blue cheese or mushrooms?
- Does your patient use mint flavored toothpaste or suck on mints?
- Is there a possible source of mold in your patient's house, such as a crawl space or damp basement?
- Is your patient exposed to any inhalant sprays or pollens?
- Does your patient take any medicines, apply any creams or powders, use eye drops, or apply perfume?

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THE BREASTS THAT NEVER STOPPED GROWING

A twenty-six-year-old woman came to us because for the past ten years she had had the strangest eruption. Her skin would raise up in waves of rope-like lesions, which were intensely itchy and at times burning. Through the years thousands of these waves had passed over her skin, which left it darkly pigmented. Only her face was clear. High-dose cortisone had been the only way to suppress the waves and the itch.

Even more impressive than this patterned eruption were her massively enlarged breasts. As she sat, we saw them extending down to rest on her thighs. They appeared to be about 20 pounds each in size. She told us that they had never stopped growing.

We knew her skin disease was erythema annulare centrifugum, the result of an immune response. We had seen it in patients with internal cancer, and we had seen it as a result of fungal or yeast infections. But why in this patient? And why were her breasts so enormous?

We hospitalized her and later studied her for months. She had no endocrine disorders, her menses were normal, and no lymphoma or other tumor could be found. Tests showed she was not allergic to any fungi, but she did have a positive L.E. test for lupus erythematosus and a large number of eosinophils (32%) in her blood. The latter spoke to the presence of an allergic reaction, and the former to a sensitization to her own tissues, an autoimmune process. Could she be allergic to her own breast tissue?

The breast biopsy showed normal breast tissue, while the skin biopsy showed a hive-like reaction. We were able to extract material from a breast cyst which contained an antigen to which she, and she alone, reacted on

skin testing. It would appear that she was "allergic" to her own breast tissue and that this was the cause of her skin problem.

A mammoplasty was done with the surgical removal of 13 1/2 pounds of breast tissue. Following this there was dramatic improvement in her skin, with fading of the inflammation, burning itch, and the recurrent waves of hive-like cords. The dose of steroids was reduced to a hundredth of her former dosage. Her lupus test reversed to normal. What was it in the breast to which she was sensitive? We don't know, but one reasonable hypothesis is that it was a mammotropic virus that was stimulating her breasts to never stop growing. Alternatively, the disease lupus erythematosus could explain all of her findings.

As we continued to treat her for the next twelve years, her lupus test remained negative. Her breasts never enlarged again and she never had recurrence of her erythema annulare centrifugum. However, her sister developed systemic lupus and died of renal failure. As to a possible viral etiology, our patient later acquired thousands of warts on her legs from shaving. Not one of twenty different treatments we tried gave her any help. It was obvious she had little immunity against the wart virus, and possibly other viruses as well.

Although excision of breast tissue proved to be the best treatment, this patient is the queen of our enigmas. Her mystery remains hidden within her breast and expressed in her skin as an indecipherable Linear B hieroglyphic.

QUESTIONS FOR THE DOCTOR:

- Does your patient have an endocrine disorder?
- Did you obtain a complete blood count?
- Did you check for lupus erythematosus?
- Did you take a careful family history?
- Did your patient have a CT scan or MRI to rule out malignancy?
- Did you check for hidden infection of the teeth, sinuses, lungs, gallbladder, gut, and urine?
- Did you check her stool for ova and parasites?

- Could your patient have candidiasis or tinea infection of the feet, nails, or groin?
- Is your patient taking or applying any medications?
- Could your patient be allergic to her own breast tissue and is there any way you could check for this?
- Have you considered mammoplasty for this patient?

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THE MINISTER'S HIVES

It seemed simple enough at first. He was a forty-year-old minister who came to us suffering from hives for the past five years. A glance at his palms and then his soles showed them to be dry and scaling. "Yes, my hands have been dry for nearly twenty years and my feet for even ten years longer." Our assumption that this was a fungal infection was confirmed by microscopic examination of the scales. It all seemed so simple. Obviously, he had become allergic to these fungi and developed hives whenever the dead fungal elements entered his blood. All we had to do was treat his hands and feet and the hives would go away. Well, griseofulvin did completely cure his decades of scaly palms and soles, but the hives paid no attention. They kept right on coming.

We then found he had developed hives when given penicillin, and thought perhaps this tied in with penicillin coming from a mold similar to the fungus on his hands and feet, which might also have produced a penicillin-like product. But his fungus infection was gone, and he took no penicillin. His case was becoming complex. He had seen an allergist who, by scratch testing, showed he was allergic to eight different foods. However, a strict elimination diet for two months did not help.

Rounding up the usual suspects for hives was to no avail. He took no drugs. His dental, sinus and chest films were normal. But back to his skin tests. An intradermal injection of trichophytin, the fungal antigen derived from the fungus on his hands and feet, within hours produced a monstrous hive which completely covered his forearm. Something in his blood was also causing hives, because injecting a drop of his own blood into his skin caused a big localized hive at that spot. The same test with

his serum was negative. By fractionating his blood we found that he was sensitive to his red blood cells, but not his serum. So, what was it?

It proved to be the mold in the air. How did we find out? We listened! He told us that within 10 minutes of a visit to the home of a church member his face and mucous membranes became very swollen and breathing became difficult. His lips were also swollen, and by morning his eyes were swollen shut. It took several days to recover. Cross-examination showed he had had no food or drink prior to or during his pastoral visit. Therefore, the culpirt must be something he inhaled. Was it perfume or a room spray? No, but he remembered the house was very damp. Then we realized it had to be airborne fungal spores in a moldy room, "relatives" of the fungus of his hands and feet. We sent his wife back with a culture plate for fungus to be left open for fifteen minutes in "the room of the crime." Numerous fungal colonies grew on it, whereas the control plate from his own living room had but few colonies.

We then did intradermal skin tests to eight species of airborne fungi. He proved sensitive to all of them, but most dramatically to the Aspergillus we had found on the culture plate. Even placing an extract of this mold on the surface of his intact skin produced a hive!

So now we knew: after he inhaled the fungal allergen it coated his red cells, making it appear he was sensitive to them, mimicking autoimmunity. That explained why injecting his own red blood cells into his skin gave a hive.

This patient's sensitivity was becoming so marked that even going down into his own damp basement was risky. His cure came when he was transferred to a new pastorate in Arizona. In the dry mold-free air of Tucson, he remained hive-free. Such a radical climate change is not always necessary. We had another patient with hives from airborne mold who was cured by selling her beautiful home in a humid wooded site and moving to the city.

QUESTIONS FOR THE DOCTOR:

- When do the hives occur and how long do they last?
- Are the hives large or small and do they have either red or white halos?

- Is your patient allergic to any medicines, such as penicillin?
- Did you examine your patient for possible tinea infection of the palms, soles, nails, and groin?
- Did you give your patient an adequate trial of oral antifungal medicine?
- Did you do intradermal skin tests for candida and trichophytin?
- Has your patient been checked for possible food allergies using skin tests and elimination diets?
- Has your patient been exposed to any inhalant sprays, including fragrances?
- Does your patient live in or visit houses with moldy basements?
- Have you checked for mold in your patient's house using fungal agar plates (fifteen-minute exposures)?
- Has your patient had intradermal tests for airborne fungi, including *Aspergillus*?
- Has your patient tried moving to a different house, motel, or climate to get away from mold spores?
- Is your patient taking or applying any medicines, including eyedrops or eardrops?

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HARDENED SKIN

"My skin is turning hard and I've been told that nothing can be done," said a seventy-four-year-old woman who had just moved to our area from the South. She had recently been carefully studied by a number of doctors during a five-day stay in a university hospital. They told her she had generalized morphea, a condition for which no treatment was known. Unlike them, we greeted her with great optimism. Surely, we could do something to stop the inexorable progress of the hardening of her skin. She did not have to be Lot's wife.

She had first noted the indurated firm areas on her chest, but they had extended in eight months to also involve her back and abdomen. Her skin felt tight and itchy. Last week her right calf also started to become involved with the firm slightly darkened patches, which now we could also detect on her right forearm and both elbows. The breasts were the worst areas, with very shiny hard skin. Her hands, feet and face were unaffected.

Her past history revealed she took no medications, had no allergies, neither smoked cigarettes nor drank alcohol, and had never had any prior skin disease. She had worked in a poultry plant dressing chickens for twenty years, but was now retired. We could elicit no history of skin trauma at her work or of any tick bite preceding the hardening of the skin. Her daughter, who accompanied her, stated that she was in good health but had experienced some memory loss in the past year.

We made a diagnosis of widespread morphea, i.e., cutaneous scleroderma. The university hospital studies had ruled out systemic scleroderma,

which may become lethal as it tightens the throat, stomach, gut, lungs, and heart.

Since we felt her condition could be the result of a spirochaetal infection similar to that causing Lyme disease, we immediately began treatment with intramuscular and oral penicillin in high dosage. Within three weeks she was decidedly better. There had been no extension of her lesions and she, as well as we, could feel softening of her skin. This was especially noticeable on palpation of the breasts.

We continued the intramuscular and oral penicillin for many months, as long as the improvement continued. By the end of a year of treatment she had virtually returned to normal skin. Then the treatment was discontinued and she was discharged from our care.

We haven't met an orphan patient yet for whom something couldn't be done!

QUESTIONS FOR THE DOCTOR:

- Has your patient had a skin biopsy?
- Has your patient had a chest x-ray and pulmonary function tests to rule out pulmonary fibrosis?
- Has your patient reported any chewing or swallowing difficulties, which need evaluation?
- Does your patient have any evidence of systemic scleroderma?
- Does your patient have any acrocyanosis or contractures of the hands or feet?
- Have you checked a urinalysis?
- Does your patient remember ever having a tick bite or leech bite?
- Have you done a blood test for Lyme disease?
- Has your patient had a recent electrocardiogram?
- Have you given the patient a one- to two-month trial of weekly intramuscular penicillin or ceftriaxone?
- Has your patient ever taken tryptophan as a sleeping medication?

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BATTERY BLISTERS

"It all began with blisters behind my ears five months ago," a sixty-nine-year-old woman told us on her first visit. It would be many visits later before we could find the cause.

She described the blisters as initially being small and very itchy. As the months went by, new blisters appeared on her face, chest and, most dramatically, over her left thigh. She had always been in good health with no prior skin disease. But two years ago she had fractured her left hip. This required extensive orthopedic care, involving screws, bone grafting with a buttress plate, and the implant of an osteogenic bone growth stimulator.

On examination the blisters were large, tense, and filled with a clear fluid, while the surrounding skin was red and slightly elevated. Rubbing the skin firmly did not produce any new blisters. This simple sign (Nikolsky) helped rule out the grave diagnosis of pemphigus.

Clinically, her problem appeared to be the blistering eruption called *"bullous pemphigoid,"* usually seen in older individuals. However, skin biopsies did not confirm this diagnosis, showing only that the epidermis was lifted off of the dermis by the blister fluid. Extensive blood studies told us that she had a very high serum level of the immune protein, IgE, seen in allergic individuals.

We were able to suppress the blisters with intramuscular cortisone shots and an oral antibiotic, but the problem was not really solved. Three years later we secured more skin biopsies, and using special stains for IgE showed large accumulations of this protein in the skin under the blisters.

It was evident that our patient's blisters were of an allergic origin. Usually, this would mean a drug allergy, but she took no drugs other than

what we prescribed. Patch tests to twenty-four allergens she could be in contact with were negative, as were intradermal skin tests with the metallic materials used in her hip surgery as well as her dental work. She was not allergic to nickel, chromium, mercury, or gold.

Through the years of treating and watching her we knew that the worst and biggest blisters always came on her left thigh. Was there something underneath this area of skin which could be causing the greatest concentration of an allergic substance, something that might correspond to the "poison ivy leaf," as it were? We knew this was not the location of the screws or the plate in her bones, metal objects we had seen cause unexplained eczema in other patients.

No, there was something else. She still had the battery there that had been inserted five years ago to electrically stimulate bone healing. It was no longer functional, and her hip fracture had long ago healed. We tried to reproduce her blisters by patch testing with the chemicals found in the battery: platinum, titanium, and silicone, but nothing happened. Still, these tests were done only on the outside of her skin, while the battery was down under her skin. We felt it simply had to come out. Those blisters crowding above it told us so.

After some reluctance, the orthopedic surgeons removed the battery. (We had to threaten to remove it ourselves.) Within three days there were no new blisters anywhere on her body. The old ones also healed and the patient remained virtually clear of blisters for the following two years. The surgeons remain dumbfounded.

And so ended our three year search for the cause of this woman's blisters. We never gave up, nor did she.

QUESTIONS FOR THE DOCTOR:

- Have you done a skin biopsy with immunofluorescence?
- Does your patient have any chronic infection, such as gingivitis, cystitis or bronchitis, which might be triggering blister formation?
- Did your patient have any surgery with insertion of metal clips prior to onset of the blisters?

- Has your patient had any broken bones requiring metallic or battery implants?
- Have you checked a serum IgE?
- Does your patient have any dental implants with metal posts?
- Have you done patch tests to check for metal sensitivity (nickel, gold, chromium, and mercury)?
- Does your patient need removal of any metallic implants and have you discussed this with a surgeon?

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HAIR LOSS AND SWOLLEN LIPS

"My hair is falling out" was the complaint of a forty-five-year-old woman. This is always a difficult challenge for us. First, is the loss real or imagined? There are at least 100,000 hairs on the scalp, and with aging we lose them insidiously. And in the case of women with bouffant coiffuring, 80,000 of these can be lost before the thinning is obvious to anyone but the patient. We have no instrumentation to accurately count the hairs. Assessment is therefore crude, unlike the precision we achieve in counting the invisible red cells in a drop of blood. The number of hairs on sample areas of skin can be counted, but is so painstaking a process as to be impractical, except in a research study of the modern hair growth stimulants, Rogaine® (minoxidil) and Propecia® (finasteride). She could and did count the hairs combed out each day. These far exceeded the normal average daily hair loss of 75 to 100.

We concluded that this patient's hair loss was real. Now came the search for why. The hair was not breaking off, nor did it have loose roots. Her root strength was good when we tugged on her hair. Under the microscope her hair appeared normal. Was it simply aging? Every single one of us no longer has the hair count of our youth. However, that hair loss is gradual and inapparent, whereas this woman knew that her hair had been thinning for only the past few months. Medications are the most common cause of this type of hair loss, and often one gets a history of a beta-blocker-type medication taken for high blood pressure, or perhaps an antidepressant, pain medication, or birth control pills.

In this patient we suspected the culprit was a special hormone-like compound, danazol (Danocrine®). It has male hormone-like actions and

often thins the hair. When we asked her to stop it, however, she said she couldn't because it had saved her life. This led us into a complex history from which we learned about her attacks of swollen lips. For the past five years she had had several severe attacks of firm swelling of her face and hands, as well as swelling of her throat. These attacks were life-threatening and necessitated hospitalization on three occasions. She was diagnosed as having angioedema of the hereditary type. Her brother, mother and grandmother had all had the same problem, caused by a lack of a vital enzyme inhibitor. The danazol she was taking had restored the inhibitor in her blood, so that for four months now she had had no attacks of the swollen lips and difficulty breathing.

We knew that patients with angioedema have attacks triggered by numerous things, ranging from fever to dental work or eating shellfish. In this patient the trigger appeared to be cold sores (herpes simplex). She remembered frequent attacks of cold sores on her lips and inside her mouth, some just prior to attacks of angioedema.

Finally, we learned that for fifteen months our patient also had been suffering from severe chronic fatigue. She required twelve to sixteen hours of sleep a day. We suspected that this, too, could be an effect of either the cold sore virus, Herpes simplex, or even the infectious mononucleosis Epstein Barr virus.

We prescribed the antiviral drug, acyclovir (Zovirax®), four times a day. Within two days the patient's energy had returned to normal. She became a whirlwind of activity, needing very little sleep. And taking the acyclovir for four months prevented further cold sores. However, her hair loss continued until she reluctantly agreed to stop the danazol. Then, within a few weeks, her hair loss stopped. With a maintenance dose of acyclovir she has remained free of hair loss, fatigue, cold sores, and angioedema attacks. Her inhibitor levels also returned to normal, so that further attacks of angioedema have been prevented. Although she needs no danazol, she must continue taking the antiviral drug, acyclovir.

Even as our patient knows acyclovir or the newer members of the drug family, valcyclovir and famciclovir are wonderfully effective in combating the Herpes simplex virus, we know its help extends to other viral infections caused by similar herpes family viruses: infectious mononucleosis and hand-foot-and-mouth disease. Just as we saw this patient totally overcome her severe chronic fatigue literally in hours after taking acyclovir, we

saw the same thing in a seventeen-year-old boy about to be hospitalized with extreme fatigue due to infectious "mono." Instead of the hospital, we advised acyclovir. Two days later he was back in the gym playing basketball.

Acyclovir is truly a drug nonpareil.

QUESTIONS FOR THE DOCTOR:

- What does your patient think is causing her hair loss?
- What prescription medications does your patient take and have you looked up each one as a possible cause of alopecia?
- Does your patient apply any patches containing hormones or take birth control pills?
- Does your patient take vitamin A?
- Does your patient use eyedrops?
- Did you do a hair pluck to see how easily hairs are dislodged?
- Did you examine plucked hairs under the microscope, checking for breakage and telogen vs. anagen growth stages?
- Does your patient have high blood pressure for which she takes a beta-blocker medication?
- Is there any family history of female alopecia as part of the aging process?
- Is the hair loss diffuse or does it have a male-type pattern?
- Was your patient ill with a high fever approximately 3 months prior to onset of the hair loss?
- Did your patient have surgery or suffer from an accident or sudden emotional shock ninety days before the onset of alopecia?
- Have you checked a "health profile" with a blood count, urinalysis, blood chemistries, antinuclear antibody (ANA), and erythrocyte sedimentation rate (ESR)?
- Does your patient have chronic fatigue or a history of viral infection?
- Could your patient have arsenic or thallium poisoning from exposure to pesticides, ant traps, or rat poison?

- What does your patient believe triggers the angioedema?
- Is there a family history of angioedema?
- Did you check her blood for C1 inhibitor (C1 INH), lacking in cases of hereditary angioedema?
- Is your patient allergic to shellfish, peanuts, or any other foods?
- Does your patient have a history of cold sores on the lips or in the mouth?
- Have you checked viral titers for herpes simplex, herpes zoster, and Epstein Barr virus?
- Have you given your patient lengthy trials of acyclovir, famcyclovir, and valacyclovir for chronic fatigue and prevention of cold sore attacks?
- Is your patient atopic, with a history of asthma, hay fever, dry skin, bee sting allergy, and/or hives?
- Is your patient dermographic?

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THE WORM FROM OUTER SPACE

"See my worm," begged a twenty-nine-year-old man. We were the fifth dermatologist that week he had consulted in his frantic search for medical help. All of the others had referred him to psychiatrists, but he knew that was wrong and he was going to prove it to me. He knew he had been infected by a worm from outer space, and was desperate for a cure, but no one would believe him.

As he unrolled the gauze from his left wrist we did indeed see *"the worm."* It was there in the skin at the flexure of his wrist, neatly surgically exposed. It was long, narrow, white, glistening and warm, recognizable as *a tendon!*

We marveled and he went on to explain that he had felt the worm moving in his skin. He quickly described how he had gone to the local surgical supply house yesterday and purchased a scalpel, forceps, and probes. At 5:00 A.M. that morning he had operated, skillfully avoiding the major arteries and veins of his wrist. Now he had proof, and, fortunately, our office staff had given him an emergency appointment.

As we listened to the story, told by this man with piercing eyes, we realized he was a special type of orphan patient. He was not orphaned by physician indifference, physician ignorance, or physician disbelief. He had been orphaned by his own noncompliance. But, why should he see a psychiatrist? Did these doctors . . . did we . . . think he was crazy?

No, we replied, but he needed special help, more than we as skin specialists could give. We told him he needed a *parasitologist* to kill the worm. And we could get him one, right away.

We then called the head of psychiatry in the hospital who said, "Sure, send him right over." It was then that we said, "***You*** come right over. He has disregarded four referrals to psychiatrists already this week. I am referring you, as a parasitologist, to him." Soon, one of his residents came with a syringe full of medicine for both the E.T. worm and the patient. The last we saw of him he was being rolled down the hall on a litter, fast asleep.

The mystery of how he was infected with a worm from outer space remains more than skin deep.

QUESTIONS FOR THE DOCTOR:

- Did you know that a caring, sympathetic doctor always provides
  the best treatment for a worm from outer space?
- Have you examined under the microscope the material brought to you by "delusional" patients?
- Have you talked to a psychiatrist about your patient?
- Have you prescribed pimozide for your patient (slowly increasing doses)?
- Don't forget to call your patient's pharmacist ahead of time to discuss the problem and prevent mention of Tourette's syndrome (for which the drug is usually prescribed).
- Is your patient depressed and in need of a mood elevating drug?
- Is your patient taking any medications, which might be causing delusions of parasitosis (cocaine, amphetamines, methylphenidate, and/or monoamine oxidase inhibitors)?

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A NEW LIGHT ON PSORIASIS

His mother brought him in for light therapy. He was eight years old and for the past year had been going to a distant skin clinic for ultraviolet light treatments for his psoriasis. The trip demanded three hours of driving three times a week. His mother finally asked, "Isn't there somewhere nearer to my home I could go to for these light treatments?" And so, he had been brought to us requesting a series of late after school appointments on Monday, Wednesday, and Friday.

We examined her son. He had extensive psoriasis on his trunk, arms, and legs, which was responding well to the ultraviolet light treatments. But, as parents, we thought of the drain of three visits each week to the doctor, even if close by. We knew there could be another way. Our research had shed a new light on psoriasis.

We explained to the mother that psoriasis has a hereditary background, which we could not alter. We explained that the silvery white scales her son shed everyday were dead flakes of his outermost skin, the epidermis. Normally, our skin sheds this dead stratum corneum invisibly because the particles are so small. They rub off in the bath or on the clothing without notice. But, in psoriasis, the epidermis is growing 10 times faster than normal, resulting in big thick white scales. The secret of treatment is to slow down the rapid division of the cells. Ultraviolet light, as well as many of the psoriasis salves used today, especially tars and cortisone, do this. The rapid cell growth also is slowed down by starvation. Psoriasis was not seen in Germany after World War I. Conversely, gaining weight stimulates the cells to grow faster and makes the psoriasis

flare. The worst case we ever saw was in a woman who gained 96 pounds during her pregnancy. Once her weight went back to normal, the psoriasis cleared completely. It is this weight loss that explains the success of the many strange diets touted to help psoriasis. After all, if all you can eat is turkey, you probably will lose weight and help clear your psoriasis.

But why are the cells in psoriasis growing at a rate as much as 10 times normal? No one knows exactly. But it could be the body's attempt to shed something through the skin, such as dead bacteria. Children, in particular, are known to develop hundreds of small ("guttate") spots of psoriasis as a result of having a "strep" throat. The dead bacteria absorbed into the blood stream might flow to the skin for so-called "transepidermal elimination." This process is enormously speeded up in psoriasis, because the epidermal cells carry their waste products out of the body in days instead of weeks.

The new light we had shed on psoriasis, and hence its treatment, was our demonstration of actual streptococci within the skin of psoriasis lesions in over half of our patients. It had taken a special stain and confocal microscopy to find them. Most importantly, these bacteria were found in all types of psoriasis, not just in the guttate type so well known to be triggered by a sore throat.

And what was our patient's history? Yes, his mother said he had frequent sore throats. The mother's eyes brightened when we said, let's skip the light and use the antibiotic. We had him take erythromycin daily, and when we saw him a month later his skin was clear. And it has remained clear all winter. With the daily antibiotics he has not missed a single day of school because of sore throats. And he certainly doesn't miss those office visits for light treatments!

QUESTIONS FOR THE DOCTOR:

- Does your patient with psoriasis have any history of sore throats or "strep" throat?
- Did you look in the mouth to check the size of the tonsils and condition of the teeth?

- Did you check for evidence of streptococci with a standard throat culture, anti-streptolysin O (ASO) titer, blood count (CBC), erythrocyte sedimentation rate (ESR) and immune complexes?
- Could your patient have hidden dental infection?
- Does your patient have severe scalp psoriasis, suggestive of a smouldering ear-nose-throat infection?
- Does your patient have oral candidiasis?
- Have you examined the perianal area for evidence of Group B streptococcal intertrigo and perianal dermatitis?
- Have you requested consultation with an otolaryngologist about possible tonsillectomy for enlarged infected tonsils?
- Have you given the patient one-month trials of erythromycin, amoxicillin, and penicillin to treat the psoriasis?

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BLACK AND BLUE SPOTS

A fourteen-year-old girl came with a history of developing large black and blue spots on her arms, thighs, and abdomen. There was no pattern to the lesions, nor could we elicit a monthly or seasonal cycle. The girl denied any symptoms of itch, tenderness or pain. She would awaken to find new ones, which then slowly faded away with a bluish, at times yellowish, color. Her parents were mystified. She had seen a hematologist, whose studies on her showed normal bleeding and clotting functions. She had plenty of platelets so essential in keeping the blood within the blood vessel walls. There was no evidence of an eating disorder which could cause scurvy from vitamin C deficiency. She did not have the black and blue spots of the thin skin of the aged. And, she did not participate in any bruising sports.

A detailed history was essential. We recalled the hurried Monday office visit of a patient worked in as an emergency after she had suddenly developed dozens of black and blue spots. We rushed her to the laboratory before closing time for a complete (and expensive) battery of blood studies. We called for the results of our "stat" bloods only to hear the technician say, "You mean the results on that patient with all the black and blue spots from white water rafting yesterday? They are normal." We went home thinking, "Why did the patient do that to us? Did she worry she had leukemia and felt we would not do tests if we were told about the rafting?"

As we continued to explore this fourteen year old's problem we wondered if she were an example of a rare autoimmune reaction, with black and blue spots caused by sensitivity to her own red cells. Skin tests with her own erythrocytes, however, eliminated this possibility.

Next we prepared to take a biopsy of the black and blue skin for a fleet of special stains and study. The patient was in the operating room. As we came down the hall to enter and glove, her ten-year-old sister volunteered essential information, better than any we could get from electron microscopy. "I know why she's black and blue." "You do! Why?" "She pinches herself." And that is what it proved to be, a factitial purpura. It was child self-abuse.

QUESTIONS FOR THE DOCTOR:

- Are your patient's ecchymoses due to trauma from a sport or recreational activity?
- Is there any pattern to the lesions?
- Are the lesions related to her menstrual cycle?
- Does she need referral to a hematologist for evaluation of a bleeding and clotting disorder?
- Do her platelets appear to be normal in number and function?
- Could your patient be allergic to her own red blood cells (autoerythrocyte sensitization syndrome)?
- Is the patient taking any medicines, such as coumadin?
- Does your patient have "fragile skin" that has always bruised easily?
- Have you checked a "health profile," including blood count, urinalysis, ANA, and ESR?
- Does your patient have loose joints suggestive of Ehlers-Danlos disease?
- Does your patient have blood in her urine?
- Could the lesions be factitial, due to self-trauma?
- Does your patient take any supplements, such as horse chestnut, aspartame, or even heroin?
- Could the lesions be a "cry for help" from a troubled child having problems in school or at home?
- Did you take a careful social history?
- Did you rule out leukemia?
- Did you give your patient a trial of oral vitamin C to stimulate collagen formation and stabilize blood vessel walls?

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THE EMERGENCY ROOM ITCH

A seventy-year-old woman was supposed to see us on a Thursday afternoon. She was coming a great distance from a nursing home and our staff had been told she had had a rash over her entire body for the two years she had been in that home. They felt it was a drug eruption and hoped we could help.

The patient failed to show for her appointment, but the following Monday morning we were called to see her in the hospital. She had been brought by ambulance four days before for emergency surgery in the middle of the night, engendered by a blood clot in her left leg.

On examination we saw a woman clawing her inflamed red scaly skin, complaining of a terrible itch: "I've had it for years. Do something!" Between her fingers we saw tiny blisters, and on her fingers there were several thread-like burrows. She had scabies, the highly contagious "seven year itch." We proved it by finding the *Acarus scabiei* itch mite on scrapings. Yes, we found out that she did not have a drug rash, but scabies. And as soon as we learned it, so did the ambulance driver and his two assistants, six nurses in the emergency room, and another nine floor nurses, as well as the vascular surgeon and three of his operating room nurses. All twenty-two were now itching, because they caught scabies from their contact with her.

Moreover, we had to call the nursing home and tell them the bad news. The scabies mite is the bête noire of nursing homes. Every one of the eighty inmates as well as the entire nursing and assistant staff had to be treated. During the two years our patient had been at the home she had transferred her brood of unrecognized mites to many others, and

they, in turn, to many others. Fortunately, this terrible itch yields to three local treatments with lindane lotion. The first to kill all the mites, the second the next day to kill any mites that were missed, and the third applied ten days later to kill the young mites hatching out of the lindane-resistant eggs in the burrows.

That happened years ago. Today we have a magic bullet for scabies. No longer do we need the messy, time-consuming, potentially toxic treatments of yore. A single oral dose of ivermectin now cures scabies. *Mirabile dictu*.

Scabies is not usually an emergency, but this time it was.

QUESTIONS FOR THE DOCTOR:

- Does your patient have terrible itching all the time?
- Does the itching get worse at night or with sweating?
- Is anyone else itching in the patient's family, friends, or caregivers?
- Have you done a thorough skin examination searching for papules, vesicles and burrows on the umbilicus, sacrum, axillae and between the fingers?
- Have you done extensive skin scrapings searching for scabies mites?
- Is the patient taking any medicines that might be causing a pruritic drug eruption?
- Have you done a chest x-ray looking for Hodgkin's disease?
- Is the patient jaundiced and have you checked a serum bilirubin?
- Have you checked for Sézary cells in the blood?
- Does your patient have any enlarged lymph nodes suggestive of metastatic cancer or lymphoma?
- Does your patient have dry skin, which could have led to "winter itch"?
- Has the patient ever had any food allergies or intolerances, such as gluten (wheat)?
- Does your patient get any relief from taking antihistamines?

- Do topical steroids or systemic steroids help the pruritus?
- Have you checked kidney function with a blood urea nitrogen (BUN) and urinalysis?
- Have you done a skin biopsy with immunofluorescence (or several if no diagnosis is obvious)?
- Was your patient traveling and sleeping in different beds prior to onset of the itch?
- Have you done an eosinophil count on the blood?
- Could your patient have dermatitis herpetiformis, with lesions typically present over the elbows, knees, buttocks, and scapulae?
- Have you given your patient a trial of dapsone?
- Have you given your patient several topical treatments with lindane lotion, crotamiton, sulfur in petrolatum, or a pyrethrin-containing cream?
- Have you notified the nursing home of the diagnosis and suggested a practical treatment?
- Have you given your patient an adequate trial of oral ivermectin (as well as all of the people who were in contact with her)?
- Have you given your patient oral erythromycin for the secondary infection caused by scratching?

47

THE SLEEPER

"My skin is becoming stiff," recounted a forty-three-year-old woman. For the past few months she had noted a woody firmness of the skin on her thighs and there were red patches on her shins which also felt stiff. Her face, hands, and feet were normal. She had always been in good health and blood studies showed only a mild increase in her eosinophilic white cells.

Clinically, we felt she had the hardened skin patches of morphea, the localized form of scleroderma. We attempted to ferret out a cause, with no luck. She was taking no medications. There had been no tick bites or even a leech bite, which had caused morphea in one of our patients. She denied infections or exposure to organic chemicals, such as polyvinyl chloride, known to harden the skin. She also did not take the drug, methysergide, notorious for its ability to indurate connective tissue. She had never had silicone breast implants, which might leak and induce sclerotic skin.

We tried both cortisone and antibiotic therapy without success, as well as topical emollients which were likewise without effect. We were still searching for a cause when the patient came in with the answer and with an apology. She had found the reason in the newspaper, learning that the FDA had banned the sale of the amino acid, tryptophan. This over-the-counter compound used by thousands to combat insomnia and depression was now linked to hundreds of cases of hardening of the skin.

Our patient's apology was for not telling us she had been taking tryptophan to aid her in falling asleep. She knew she had been repeatedly quizzed by us as to whether or not she took any medications, even aspirin.

To her way of thinking, tryptophan was outside the realm of medication, being only a dietary soporific.

Our patient was a victim of a brand new disease. Tryptophan had always been considered a harmless food supplement, and was a component of many dietary supplements. Only recently did it become general knowledge that it was a precursor of the neurotransmitter, serotonin. As such, it is really a full-fledged drug, since serotonin released at our nerve endings controls our moods and our sleep patterns.

From across the country came an ensuing series of reports linking L-tryptophan ingestion to not only hardened skin patches, but also muscle pains and nerve damage. The seriousness of our patient's disease was underscored by the report of at least twenty deaths. In all, the cardinal finding was an increase in the eosinophils in the blood, exactly as we had found in our patient.

The fact that a simple protein derivative could induce such havoc in the connective tissue throughout the body had a chilling effect on the acceptance of alternative therapy. These dietary supplements, herbs, and aromatics appear so innocent, natural, and safe. However, they have never been subjected to the rigorous testing required by the FDA for drugs. In this case, the testing was done by an unknowing public and a contaminant of tryptophan was found to be dangerous.

Our patient stopped her tryptophan the day of the news release. Since then she has slowly improved. Hers was a case of diagnosis and cure by the daily newspaper.

QUESTIONS FOR THE DOCTOR:

- Have you done a skin biopsy of an indurated area, searching for morphea and eosinophils?
- Has your patient ever had trouble sleeping, so that she takes a sleeping pill or health food supplement?
- Has your patient ever taken L-tryptophan?
- Did you check your patient's blood for eosinophilia, including an eosinophil count?

- Does your patient remember having any tick bites or fly bites?
- Has your patient ever visited or vacationed in wooded areas where Lyme disease is common?
- Have you done a blood test for Borrelia burgdorferi or any other Borrelia species?
- Has your patient ever gone swimming in leech-infested lakes or rivers, and was she bitten?
- Has your patient ever worked around polyvinyl chloride or other organic chemicals?
- Has your patient ever had silicone breast implants or any silicone implants elsewhere?
- Did your patient receive any benefit from penicillin or ceftriaxone injections every two weeks for three months (based on the supposition that she has morphea possibly caused by Borrelia infection)?
- Have topical steroids helped your patient?

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A CRAZY RASH

A sixty-six-year-old woman came fully frightened. She had been told that her rash could be mycosis fungoides, a rare form of malignant lymphoma. The diagnosis had been made on the basis of skin biopsy findings.

She related to us her eighteen-month history of a scaly, mildly itchy eruption. It had begun on her breasts, spreading later to her back, abdomen, and thighs. At first her condition had been called parapsoriasis, but a second skin biopsy suggested that the problem had become malignant, converting the diagnosis to mycosis fungoides.

Treatments had included cortisone preparations, both internally and externally, antihistamines, and the avoidance of bathing (which magnifies itch). Nothing had helped. She still had large red scaly patches on her trunk and thighs. We felt she had the benign parapsoriasis, and not the dreaded mycosis fungoides, which insidiously leads to skin tumors and eventually spreads internally.

Since there is no known cause of parapsoriasis, it is labeled "idiopathic." A century of looking for causes of parapsoriasis had yielded no answers. It would have remained that way in our patient, but for our detective work. Actually, nothing blunts a doctor's zest for studying a patient more than a dermatosis known to be idiopathic.

But nothing occurs without cause, and elimination of the cause spells cure for disease. We, therefore, always zestfully hunt for a cause. Our most successful maneuver has been to look for foods, bugs, and drugs that might be incriminated. However, this time we had no score after months of probing a mounting database, repeated history-taking, antibiotic trials, and food and drug eliminations.

We then looked for the unusual. This patient told us she strengthened her brittle fingernails with tea bag paper glued onto each nail plate and then applied colored nail polish over the paper. With mounting interest we learned that she had begun this treatment program shortly before the appearance of her eruption and had used it ever since.

We began to suspect her parapsoriasis just might be due to an allergy to this special nail treatment. Patch tests had already shown that she had no allergies to twenty-nine of the most common troublemakers that patients come in contact with. She was not allergic to the nickel or gold of jewelry, or the epoxy resin in glues. Now with patch testing we found she was also not sensitive to any of her four nail enamels or the tea bag paper.

But, yes, it was the ethyl cyanoacrylate glue (Krazy Glue®) she was using to attach the paper to her nails! This dried glue produced blisters when kept on her skin in a patch test for forty-eight hours. She was exquisitely sensitive to a product which, up until then, had a blemish-free history. It had never been known to induce an allergy despite its use by millions of people around the world. Control patch tests on four volunteers were totally negative. A second nail product containing ethyl cyanoacrylate, called "5 Second Nail Glue," also produced the same severe eczematous reaction on patch testing.

After our patient removed the Krazy Glue from her nails with acetone and stopped its further use, her eruption cleared in one month. Since it takes thirty days for the epidermis to be shed, every month we have a totally fresh new outer skin. For that reason we tell our patients, treat your skin like a baby. It is only thirty days old. Parenthetically, the dermis, made up of collagen, takes as much as seven years to recycle.

With a fresh new epidermis our patient continues to wear a variety of nail polishes, applying the tea bag paper to her nails using the polish instead of glue. There has been no recurrence of her "nearly cancer" rash for the past two years.

By being curious we had shown that the century old riddle of parapsoriasis probably has many answers. We had simply shown one of them. But we had also demonstrated for the first time that ethyl cyanoacrylate could cause a dermatitis. Since then more than a dozen examples of this "crazy" eczema have been described.

QUESTIONS FOR THE DOCTOR:

- What does the patient think caused her skin problem?
- Have you done multiple skin biopsies in an effort to rule out mycosis fungoides?
- Should further histologic diagnostic techniques be used searching for mycosis fungoides, including electron microscopy, DNA cytophotometry, and T-cell receptor gene arrangement?
- Have you looked for Sézary cells in the blood?
- Have you made a thorough search for possible chronic internal or external antigen exposure?
- Have you questioned your patient about cosmetic use, including perfume, toothpaste, shampoo, soap, hairspray, and nail polish?
- Has your patient had any surgical procedures or broken bones, which might have resulted in metallic implants or surgical clips?
- Has your patient had any major past illnesses, which could still be smoldering (e.g., bronchitis or pneumonia)?
- Have you searched for hidden infection which might induce parapsoriasis, including cold sores, tonsillitis, cholecystitis, dental problems, sinusitis, hepatitis, cystitis, candidiasis, and tinea pedis/unguium?
- Did you check for intestinal parasites?
- Have you taken a detailed drug history at each visit, including prescriptions, herbals, supplements, vitamins, topicals, douches, eye drops, cough drops, and sprays?
- Could your patient have an atypical form of scabies?
- Have you had your patient stop all cosmetics, fragrances, and nonessential medications?
- Have you stopped *all* medications for at least four weeks?
- Have you given the patient three-week trials of various oral antibiotics, antifungals, and antivirals?
- Did you give your patient a trial of oral ivermectin?

- Did you do extensive patch tests searching for contact antigens, including epoxy and cyanoacrylate glue?
- Does your patient have a normal CBC, ANA, UA, and chemistry profile?
- When did the skin problem start and what else was going on health-wise in the patient's life at that time?
- When does the itching get worse?
- Does your patient use aromatherapy or scented candles?
- Did you check on your patient's diet, searching for ingestion of sensitizers, such as shellfish, nuts, diet drinks, and blue cheese dressing?
- Does your patient have contact with photosensitizing fruits or vegetables, such as lime, parsnips, dill, and celery?

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BALD SPOTS

"His scalp is showing" was the delicate phrasing of a ten-year-old boy's mother. We learned that three months ago he had developed three perfectly round areas of perfectly bald skin on the right side of his scalp. They were totally symptomless, and not inflamed, looking like totally normal skin. Around the edges we could see tiny short hairs that looked like exclamation points. These helped confirm the diagnosis of alopecia areata.

The hair had simply suddenly fallen out without a trace. This was not the hair loss of lupus erythematosus, which is inflammatory, or the hair loss of ringworm with its broken hairs. This was not the hair loss of trichotillomania where the child plucks out his own hairs in frustration, leaving a tell-tale stubble of very short hairs (too short to pull).

No, this was an autoimmune condition known as alopecia areata. Somehow, the body rejects the hairs without any sign of obvious inflammation. As the hair follicles stumble to recovery around the edges, short atrophic exclamation point hairs are produced, constricted at the base in a sputtering regeneration.

We did not need a skin biopsy for diagnosis, but we needed to study him for a cause. Although alopecia areata is classified as an autoimmune disease, and thus a rejection phenomenon, we know from experience that a focus of infection may trigger such hair loss. What was this boy's source of infection? We did not have to look far. He had developed a severe ear infection on that same right side about three months ago. We reasoned that the bacterial products had traveled up the right side of his scalp, possibly through the nerves, and attached to the pigment of his

hair bulbs. Possibly, he might be allergic to this bacterial material, with his body shedding the hair to rid itself of this foreign material.

We postulate that the melanin pigment of the hair is a trap for the bacterial products, since in older patients the dark hairs are shed, not the white hairs. Because the hair loss is very rapid this would explain why some people turn white over night. They have lost the dark hairs and now have a head of "thin" white hairs.

Our patient was given intensive antibiotic therapy and now, a month later, new hairs are appearing. He will need long-term antibiotic treatment, and possibly "tubes" in his ears. We have referred him to an ear, nose and throat specialist.

We like to think of alopecia areata as a special type of autoimmune disease which we call an auto-bacterial-immune disease. We always look for an associated focus of bacterial infection near the patches of overlying hair loss. We have found it in the ears, teeth, gums, throat, lungs, and bladder. The value of looking closely is highlighted by our patient who had bald spots in his pubic hair. He was found to have chronic infection of the prostate located just below the areas of hair loss.

QUESTIONS FOR THE DOCTOR:

- Could the child be pulling his hair out, sometimes evidenced by finding hairs in the bed?
- Does the child have any psychological problems evident at home, school, or church?
- Has the child had any chronic or recurrent problems involving his tonsils, ears, teeth, or sinuses?
- Did you look in his throat for evidence of enlarged tonsils and ears for signs of otitis media, which could harbor "silent" infection?
- Have you done lab work, including a CBC, antistreptolysin O titer (ASO), urinalysis, and throat culture?
- Has your patient had good dental care, with no evidence of dental abscess, caries or gingivitis?

- Have you asked for an otolaryngology consultation with consideration of ear tubes or tonsillectomy?
- Have you done a hair pluck to examine the hair bulbs?
- Can you see exclamation point hairs?
- Has your patient been exposed recently to anybody with a "strep" infection?
- Have you given your patient one-month trials of oral penicillin and erythromycin?
- Does your patient get cold sores, and if yes, have you given a one- to two-month trial of oral acyclovir?

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THE DOG DIED

"It began on my left breast two years ago," recited a seventy-six-year-old woman. It looked like ringworm, but it wasn't. Today she had extensive large, red, circular plaques on her left breast, right armpit, both thighs, and the groin. The borders were rimmed by thickened red skin.

She had never had skin disease before, but she was sensitive to sulfonamide and tetracycline medications. She was taking five different pills for heart disease. Nothing had helped her skin.

Our examination revealed no fungi on skin scrapings, and a skin biopsy confirmed our clinical diagnosis of granuloma annulare. This ring of cord-like chronic inflammation is a strange skin reaction with many different causes. We have seen it from yeast infection, but anti-yeast medication did not clear hers. We have seen it disappear completely simply as a result of taking a skin biopsy, but no such luck for her. We also have seen it from a focus of bacterial infection, but even our best antibiotic for cystitis did not prevent new lesions from appearing on her skin. Her blood studies were normal and gave us no clue as to where to turn.

We tried another antibiotic, and yet another, to no avail. There were new lesions on her left forearm. They were mammoth. We tried suppressing her immunity with no help. We now found that she had developed diabetes and hoped her internist's treatment for this would help, but it did not.

She entered the hospital for surgery on her spine. Within a month her skin had returned completely to normal for the first time in three years. But only a month later we were crushed to see it explode back out.

We had now chased her skin disease for over two years. We had not given up, but we could have, for serendipity was to step in and succeed where we had failed.

The patient called and said, "I have a surprise for you. I am clear – all clear." She came in, fortunately, or we would have always doubted she was really clear. We would have felt maybe she just wanted a new doctor and didn't want to hurt our feelings. But, come in she did and her skin, her entire skin, was totally normal. Bursting with curiosity we said, "What did it?" She simply replied, "The dog died!"

We then got this latter day history. Her dog, a black Labrador, had died five weeks ago and her improvement began shortly thereafter. Now it was complete. She pointed out that for three weeks last summer when she had cleared she had been in the hospital and at her daughter's home, totally away from the dog.

The dog died. Why was this her cure? Our patient had raised him from puppyhood and had slept in bed with him every night for seventeen years. After thirteen years had something changed? What happened in the thirteenth year? Had she become allergic to her dog? She used no sprays on the dog. Patch tests to dog hair and to dog saliva were negative, as was a blood test to dog dander. We suspect she had become sensitized to an inhalant allergen in her dog's breath. After all, she had close exposure to his breath eight long hours a night for many years.

Was she really sensitive to her dog? It was too late to find out. His burial had been weeks ago.

Our Sherlock Holmesian curiosity died with her cure. We now regret that we did not follow one more lead. Was she allergic to the dust from the dry food she fed her dog? Inhalant allergens are stealth pathogens. Another of our patients would never have been cured until her gold fish died but for the fact that we proved she was allergic to the powdered food she sprinkled in their bowl.

QUESTIONS FOR THE DOCTOR:

- Did you do a KOH prep and fungal culture to make sure your patient didn't have tinea corporis?
- Since the lesions started on her upper trunk, did you obtain a chest x-ray to search for nearby "underlying" pathology?
- Did you do a skin biopsy with special stains for mycobacteria (acid fast and atypical)?
- Did you culture skin biopsy specimens for bacteria, fungi, and mycobacteria?
- Did you take a careful history looking for chronic or past bacterial, viral, and fungal infections?
- Did you do a PPD and inquire about possible exposure to tuberculosis?
- Does your patient have any pet birds or has she ever worked around wild birds, chickens, or other poultry?
- Did your patient grow up on a farm?
- Does your patient have any pets, including fish?
- Does your patient sleep with any pets?
- Is your patient allergic to any foods, drugs, pollens, or animals?
- Has your patient ever traveled outside of the country?
- Did you check a CBC, chemistry profile, and UA?
- Does your patient have diabetes or a family history of it?
- Did you try stopping her medications one at a time for three-week periods?
- Does your patient get yeast infections or cold sores?
- Have you prescribed one-month therapeutic trials using various oral antimicrobial agents, including clarithromycin, ketoconazole, acyclovir, and metronidazole?

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THE ABACUS TUMOR

"What is this thing that moves up and down my arm?" asked a seventy-six-year-old retiree. He demonstrated a little lump under the skin of his left forearm. He moved it first down near his wrist and then way back up his arm. It could travel about 8 inches, just like an abacus bead. He told us he had played with it for about six months. It was a painless firm lump, about a half inch in diameter. There was no sign of inflammation. His health was excellent.

We were totally intrigued, having never seen a mobile tumor. We felt that it must be a foreign object, but he denied any history of bullet or shrapnel wounds. He had no knowledge of glass having penetrated his skin. We thought of a patient of ours from whom we extracted a six inch plant stem from her foot. She had been hiking in Scotland in open sandals and had no knowledge of how the stem had gotten into her skin. Surely, this man's tumor must be an inert foreign mass. Or could it be a parasitic larva that had died in the skin and become enclosed in a fibrous movable caul? Could it be a strange rheumatoid nodule? He did have arthritis of his left wrist.

We knew this mystery would be easy to solve. There was no need for a dazzling differential diagnostic list of twenty diseases. It was a *vignette á clef* where biopsy was the key. We held the abacus bead firmly while anesthetizing the skin, not wanting it to slip away from our scalpel. But there it was just under the skin, a small firm yellow ball with an umbilical cord of fibrous tissue. So it was "alive," but was there a foreign body within? No, under the microscope the playful little friend was pure fat. There was no cancer. It was a fat lobule that had broken loose, attached only by its

blood supply. Apparently, the patient had massaged it so carefully that its vascular tether grew longer and longer, permitting it to wander in the underworld of skin.

The patient returned to have the sutures out. He was satisfied his mystery had been solved, but as he left he said wistfully, "I do miss my worry bead."

QUESTIONS FOR THE DOCTOR:

- Did you excise the tumor for histologic diagnosis?
- Did you reassure the patient that the fatty tumor was *not* cancer?

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NO SPIT

"I can't spit, my mouth is so dry," was the complaint of a fifty-six-year-old man. He told us he had had a dry mouth for the past few months. As an executive in a large corporation he had noted difficulty in speaking, as his tongue and lips were very dry. His dentist was concerned about the appearance of caries, and food had little taste. There was none of the normal salivation upon seeing, smelling, or tasting his favorite foods. Dry food was hard to swallow. He was often at the drinking fountain and was frequently sucking on lozenges, to little avail. Even sourballs, which increase salivary flow to twenty times normal, gave only temporary relief.

All this confirmed the diagnosis of *xerostomia*, or dry mouth. Normally, he should be secreting over a quart of saliva every day, mostly during the daytime. However, we estimated he was putting out barely a tablespoonful. It is saliva that enables smooth tongue movements and lip motion, important in enunciation. It is also saliva that aids in the tasting and swallowing of dry foods. And it is saliva which flushes and degerms the teeth, preventing caries. Saliva contains the same germicidal lysozyme found in tears to protect the eye, as well as antibodies and other antibacterial chemicals.

But why did this man have a dry mouth? It was not the dry mouth of the fearful public speaker, which passes once the person is off stage. His problem was continuously present, and he denied any special stress in his family or business life. It was also not the dry mouth which is a common side effect of many drugs, because he was not taking any medications.

We had to look deeper. The triple pairs of salivary glands which keep the oral cavity moist are under the control of autonomic nerves,

which do not obey conscious commands. It is the primitive nervous system which protects us. The salivary glands respond to both sympathetic and parasympathetic nerves, quietly serving this autonomic system. It is the sympathetic fibers, so active in the fight or flight reactions, that inhibit saliva formation. These fibers, in turn, are affected by centers in the cerebral cortex and salivary centers in the brain stem. But we could find no fault here. His neurologic examinations were normal. He had had no accidents, trauma, x-ray treatments, or surgery that could have damaged the parasympathetic fibers that stimulate saliva secretion.

But could he have a disease? Again, the answer was no. He had no salivary duct stones. A biopsy of the salivary glands showed them to be normal, ruling out sarcoidosis and the rare Sjögren's syndrome with dry mouth. Nor did he have any dryness of his eyes, so typical in Sjögren's syndrome. He was in perfect health with no trace of diabetes, a disease known to disrupt the autonomic fibers and lead to local absence of sweating.

We simply could not find the cause of his spitless state. Nor could we give him much relief. Even pilocarpine, the drug that mimics parasympathetic nerve stimulation of the salivary glands, was not dramatically helpful.

The denouement came while we were still struggling for a cause and a cure. It came when we saw his picture on the front page of our morning newspaper. He had been indicted for leading his corporation into bankruptcy. His months of hidden stress were undoubtedly the cause of his dry mouth. We suspect his lawyers provided him with the cure and that once free of the charges he will be able to spit again.

QUESTIONS FOR THE DOCTOR:

- Did you take a thorough drug history searching for possible causes of xerostomia, such as antihistamines, diuretics, bronchodilators, antidepressants, or anticholinergics?
- Did you check your patient for Sjögren's syndrome, including an ANA, Anti-Ro (SS-A) and Anti-La (SS-B) antibodies?
- Is your patient under increased stress, either at home or at work?

- Is your patient frightened about something?
- Could your patient be addicted to morphine or codeine?
- Is your patient trying to stop smoking using a nicotine patch?
- Is your patient taking St. John's wort or any other herbal supplement?
- Does your patient have to continuously chew gum or suck on candies or lozenges to produce saliva?
- Did you seek ophthalmologic consultation concerning possible dry eyes?
- Does your patient use eye drops containing timolol?
- Does your patient use a nasal decongestant?
- Does your patient take antacids containing loperamide?
- Does your patient have trouble sweating, leading to heat intolerance?
- Did you examine your patient's tongue and lips for signs of cheilitis and lingual papillary atrophy?
- Have you given your patient a trial of oral pilocarpine (Salagen® tablets) to help restore saliva production?

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THE SMELL OF BURNT TOAST

"I don't have a skin problem . . . but I was told you might help. A few months ago I woke up smelling smoke. But there was no smoke and ever since then everything has smelled like burnt toast," was our introduction to a seventy-one-year-old woman. She went on to explain that this perception of the aroma of burnt toast was continuous, twenty-four hours a day, week in and week out. It seriously depressed her appetite. She no longer enjoyed food, although her sense of taste was perfectly normal. She had already lost 10 pounds in weight.

It wasn't that she had lost the sense of smell, but instead was a case of misidentification of odors. Even as people are color blind, she was odor blind. All stimuli of smell evoked only the smell of burnt toast, including coffee, onions and cantaloupe. The more powerful the stimulus the more intense the odor of burnt toast. Her medical diagnosis was *dysosmia*, or as some prefer to call it, *parosmia*.

The diagnosis was easy, but what caused this sudden malfunction of an organ which, in its own way, is as exquisitely specialized as the eye? The organ of olfaction is located in a patch of specialized mucosa high in each nostril. It is truly remarkable, for there, totally hidden from view, are over 10 million separate bare nerve endings. They are actually outside the body, unlike any other nerve. Amazingly, they are the only nerves in the body that die and regrow anew every thirty days. Surely, learning their secret of regeneration might bring hope for paraplegics needing regeneration of new nerves to revitalize their legs.

Protected only by mucus, these nerves are stimulated by the chemicals reaching them. Thus, sniffing is essential for detection of traces of the

gases or liquid droplets in the air around us. Nerve impulses from these stimulants pass a short distance into the skull at a processing center, called the olfactory bulb. Normally, at this point each of the thousands of odors we recognize fires off specific relay neurons, which pass the impulse on to the uncus in the lower part of the brain. If any electrical circuit misfires in this area, the person experiences sudden episodes of abnormal smells, termed "uncinate fits," similar to an epileptiform seizure.

The odor informational pathway further travels through the frontal lobes of the cortex and the basal regions of the brain. In the limbic or border zone odor impulses evoke memories and emotions, so central in Proust's classic novel, *Remembrance of Things Past*. All these pathways impinge on the hypothalamus, the major control center for both appetite and emotion.

Smell is the least understood of our senses. Its subjective nature makes it difficult to study, but we do know many causes of the dysosmia our patient suffered. By a layered history, i.e., one thick layer from each office visit, and from tests, we could rule out the common causes. She had had no injury or fall to explain her problem. Nor did she suffer from either Alzheimer's disease or Parkinsonism, both associated with puzzling parosmias. Furthermore, it was not a drug side effect or the result of an infectious disease. It was also not the sign of depression, as our patient was unhappy only over the "burnt toast" that had entered her life. We were able to rule out hallucinations as a cause by giving her the drug, pimocide, so famous for removing delusions of parasites in hallucinatory patients. It had no effect.

We further explored making a diagnosis by drug trials. Again, failure. Drugs that knock out allergic reactions, such as antihistamines and cortisone, had no effect. Medicines that affect neuronal transmission, such as anticholinergics, produced no change. Antibiotics and antivirals, as well as vitamin A, vitamin B_{12}, and zinc were not helpful.

The search went on. We learned that her nose, throat, teeth and ears were normal, as well as her neurologic examination. Her blood studies showed no thyroid malfunction, no immunity problem, no disease. Her sinus x-rays and skull x-rays were equally uninformative. She had normal carotid artery circulation to the brain as shown by Doppler studies. An electroencephalogram showed no changes, even on challenge with the aromas that evoked strong burnt toast sensation.

The answer came with the MRI (magnetic resonance imaging) scan of her brain. There the radiologist saw focal areas of high signal density in the cerebral hemispheres. These were infarcts, small areas of vascular shut down. Our patient had apparently suffered an "olfactory stroke" that morning she first smelled smoke but there was no smoke. Now we knew why the onset was so sudden. Incidentally, the MRI scan showed normal olfactory nerve tracts.

Our patient was unique in having had a stroke so tiny it affected only her sense of smell. She had not lost control over her muscles, speech, or cognition.

Knowing the cause, we realized the "burnt toast" smell would be with her forever. Yes, we explained it would be forever unless she had the nerves cut, making her completely anosmic, with no sense of smell. This she declined. She had already lost the primitive pleasures of the nose: the fragrance of flowers, the bouquet of wine, and that smell of roast turkey. To completely denervate the olfactory epithelium would rob her of any protective function of the nose. At least she still has an alarm system that works, even though it does not work exactly right. Besides, she said, "Losing weight isn't all bad."

QUESTIONS FOR THE DOCTOR:

- Does your patient have sinusitis, tonsillitis, rhinitis, or an upper respiratory infection?
- Has your patient had a CBC, UA, chemistry profile, and thyroid studies checking for hypothyroidism?
- Has your patient consulted an otolaryngologist?
- Is your patient taking any drugs which might cause parosmia, such as terbinafine, nifedipine, aminophylline, or chlarithromycin?
- Could your patient be having hallucinations due to schizophrenia?
- Has your patient ever had a head injury or suffered a recent fall?

- Has your patient been exposed recently to solvents, such as paint strippers?
- Could your patient have a brain tumor affecting the hypothalamus?
- Does your patient have normal carotid artery studies?
- Is your patient depressed and did you try treating her with an antidepressant such as amitriptyline (Elavil®)?
- Does your patient have any signs of Parkinsonism or Alzheimer's disease?
- Has your patient recently had the flu?
- Has your patient consulted a neurologist or neurosurgeon?
- Could your patient have suffered a stroke?
- Would your patient benefit from a PET (positron emission tomography) scan?
- Has your patient had an EEG with a large olfactory component searching for uncinate seizures?
- Has your patient had a CT or MRI scan of her brain?

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THE TWENTY-THREE YEAR ITCH

"Can I get off cortisone?" was the plaintiff plea of this new patient. "It makes my face so puffy." She was fifty-one years of age and had suffered a terrible widespread itch since she was twenty-eight years old. It tore holes in her stockings. It kept her awake nights.

She had been told it was due to stress. She was serving on too many committees. "Relax and the itch will go away," but it did not. It followed her to what should have been pleasant carefree Caribbean vacations. It followed her on her move halfway across the country to a new home. As we watched her scratch, we realized it had followed her into our office. Topical creams, lotions, and sprays were only momentary distractions. Her fingernails were polished from incessant scratching. And, the more she scratched, the more the new spots appeared.

There was no mystery as to her diagnosis. She had generalized lichen planus, now a twenty-three year itch. It had been repeatedly diagnosed clinically and histologically by a half dozen doctors. She had been told that no cause is known and cortisone could give her relief. And it had, but she wanted to escape the side effects of the cortisone she had been taking for so many years. Despite her edematous face and the bulge on the nape of her neck, we could find none of the more serious side effects of cortisone, such as hypertension, peptic ulcer, or osteoporosis. There were no black and blue marks on her skin or thinning of the skin from the potent topical steroids she had used.

There was no mystery as to her diagnosis, but what was the cause? Lichen planus is a unique pattern of skin disease which, like hives, has many different causes, usually only one for each patient. The pattern of

skin change is remarkably distinctive and favors the rapid (1/25 of a second) "augenblich" diagnosis. The spots are small shiny purplish bumps (papules) with perfectly flat tops and angular edges. Hence, the dermatologist's alliterative nmenonic: *purplish, pruritic, polygonal, planar papules*. Our patient had all of these signs "in spades."

But why? We knew we must look within. "Do you mean to tell me skin diseases can come from something inside?" We replied, "Yes, we do. No skin is an island." It was a new thought for her and, no doubt, for some of her previous doctors. We had recently cured a little seven-year-old boy who had had lichen planus for over five months. The cure came with the discovery on stool examination of an intestinal infection, giardiasis. A single two week course of Flagyl® eradicated the parasite, G*iardia lamblia*, and cleared his skin. Not all causes of lichen planus are so easily removed. For example, the hepatitis C virus is currently beyond our therapeutic reach.

But what was the cause in our patient? The answer came not from sophisticated tests, but from simply asking endless questions. She indicated that she had had a lifelong history of chronic infection of her urinary bladder, treated innumerable times with ten-day courses of antibiotics. At first she took sulfa, but after several years became allergic to it, developing large hives atop her lichen planus. For the past fourteen years she had taken multiple short courses of nitrofurantoin therapy.

Her cystitis was now the centerpiece of our therapeutic attack. We knew that the urologists and gynecologists she had consulted were satisfied when their ten days of antibiotic therapy rendered her urine sterile on laboratory culture. But, we knew one thing more – that the bladder mucosa was still coated with residual bacteria. These bacteria, the cause of her itch, were not washed off with urination any more than bacteria can be totally flushed off one's skin by washing. To rid the skin of bacteria with soap, water, and brushes, one has to scrub the skin as the surgeons do. But, we can't scrub the inside of the bladder. The answer, therefore, lies in long-term day in, day out, antibacterial therapy.

We looked for the ideal antibiotic. We stopped the cortisone and began two week trials with penicillin, erythromycin, and several other drugs. There was no effect. We even tried therapy for yeast using ketoconazole, again without help. Finally, the magic bullet proved to be Flagyl®, an antibiotic that in two weeks produced the greatest improvement in her skin she had experienced in three years. We were jubilant and asked her to continue it for two months. In that time the bladder mucosa should be

shiny new and free of bacteria. She finally stopped the drug and remained completely free of all papules and itch . . . but for just three months. Then the lichen planus began to creep back. Again, it resolved with another month of Flagyl® therapy. We now realized that our patient's natural immune responses were inadequate and she was advised to remain on daily prophylactic nitrofurantoin indefinitely. A year later she reported she had been itch-free all that time. Nor had she had any more attacks of cystitis and nary a single spot of lichen planus.

When it comes to reaction patterns in the skin, forget the salves and look within.

QUESTIONS FOR THE DOCTOR:

- Was your patient taking any medications when she broke out the first time?
- Does your patient have lichen planus or a lichenoid drug eruption?
- Have your done a skin biopsy?
- Does your patient have lesions localized in areas of trauma (Koebner phenomenon), indicative of circulating antigen?
- Is your patient taking any medicines which might induce a lichenoid drug eruption, such as methyldopa, spironolactone, omeprazole, or quinine?
- Is your patient getting gold therapy injections?
- Does your patient have gold fillings in her teeth and have you done patch tests for gold sensitivity?
- Could your patient have a chronic urinary tract infection with intermittent symptoms of cystitis?
- Have you searched for other occult infections?
- Have you examined your patient's feet for chronic tinea pedis and onychomycosis?
- Have you checked your patient for hepatitis C?
- Did you put a drop of mineral oil on the papules to search for a white lacy pattern (Wickham's striae), diagnostic of lichen planus?

- Does your patient work with color film developing photographic chemicals?
- Have you done patch tests for epoxy, nickel, mercury, copper, and paraphenylene diamine, as well as gold?
- Could your patient have a lichenoid contact dermatitis from touching or wearing black stockings dyed with paraphenylenediamine?
- Did you look in your patient's mouth for the telltale lacy white pattern on the buccal mucosa?
- Did your patient benefit from therapeutic trials of PUVA and/or systemic steroids?
- Did you search for ova and parasites, such as *Giardia*, in the stool?
- Has your patient traveled in the tropics or subtropics, with exposure to biting insects?
- Does your patient have digestive problems such as diarrhea, which could be indicative of a parasite infestation?
- Has your patient eaten raw fish or drunk from any mountain streams?
- Did you treat your patient for possible occult infection with three-week trials of metronidazole, trimethoprim-sulfamethoxazole, dapsone, griseofulvin, itraconazole, minocycline, and clarithromycin?

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THE MYSTERIOUS TREATMENT

"What can I do? What can I do?" came the sobbing voice over the telephone. It was a former patient of ours. "What can I do?" she continued, "My mother has pemphigus with blisters all over her body. Her doctors tell her she will die if she doesn't have treatment." "So?" we replied. "But, my mother won't accept any treatment, since it's against her religious beliefs. Last year she had a blood clot and lost her leg because she would not allow any treatment. What can I do?" We tried to calm the daughter, telling her we would see what we could do. "Tell your mother I would like to see her as a friend, not as a patient. Just bring her over for a chat."

The next day in came the daughter with her mother. As we sat in the consultation room, the tears were rolling down the daughter's cheeks. And clear fluid was dripping down the mother's leg from large open blisters. Indeed, the dye from her purple shoes was being leached out onto our carpet.

The mystery was, how to treat this little old lady so she could hold onto life ***and*** her religious beliefs. The epiphany came in a flash as we began talking about the dye on our carpet. It was then that we saw a magic carpet of therapy. We said to the mother, "We see that your daughter is very sick. May we help her?" The mother gave a wan assent. "We can help, but the medicine we have to prescribe for her must be taken by you. All right?" There was no answer, but we suggested she talk to her spiritual advisor.

Several days later the two of them came back. "Yes," the mother said, "My spiritual advisor said I can take the medicine if it is to treat my daughter and not me." We carefully wrote out a prescription for cortisone and gave the daughter exact directions.

When we saw them again in a week, we simply asked the daughter how she felt. And as the daughter improved we gradually, over a period of months, reduced the number of friendship visits while tapering the dose of cortisone downward. Never did we examine the mother. Never did we do blood counts, skin biopsies, or special laboratory studies. The daughter was the patient. The mother remained simply a part of a *modus vivendi*. She was the essential route for administration of medicine for her "sick" daughter.

As the mother's blisters dried, so did the daughter's tears. Our friendship practice, far from the rigors of scientific and religious dogma, had made everyone happy. And, it is no mystery that that's what medicine is all about.

QUESTIONS FOR THE DOCTOR:

- Are there other ways to give your patient medicines she doesn't want to take due to religious beliefs?
- Have you consulted the patient's spiritual advisor about possible therapy, which could be life-saving?
- Could your patient have paraneoplastic pemphigus caused by an occult neoplasm?
- Could your patient have pemphigus caused by hidden infection?
- Did your patient ever take penicillamine, penicillin, ampicillin, ibuprofen, isoniazid, or rifampin, which can induce pemphigus vulgaris?
- Is your patient a heroin addict?
- Does your patient eat a lot of onions, garlic, or other thiol-containing foods or drugs, which may worsen pemphigus?
- If your patient needs long-term, high-dose steroids for control of pemphigus, would it be safer to add other immunosuppressants, such as azathioprine, methotrexate, cyclophosphamide, or mycophenolate?
- Have you given your patient three-week trials of tetracycline or dapsone?
- Would your patient benefit from treatment with intravenous immunoglobulin (IVIG)?

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THE CREEPING ACNE CYST

It seemed to be an ordinary case of acne. A nineteen-year-old boy had numerous blackheads and pimples, as well as small scars, evidence of former battles fought in his skin down through the adolescent years. We knew it was the *H & H* disease, due to *hormones and heredity*. The androgens were pumping up oil production in the sebaceous glands of the face, while at the same time blocking its flow to the surface. The blockage was produced by plugs of dead horny cells, seen as blackheads but known scientifically as *comedones*. The name derives from the Spanish word for worms and, indeed, as we press them out, they look like little black worms. The black color is not due to dirt, but simply comes from a darkening of the plug due to oxidation. Scrubbing won't remove them any more than sanding a board will remove a nail. Each comedo is deep in the pore of an oil gland. At the time we prescribed vitamin A in large doses to promote shedding of these stagnant cells. Now, we would have prescribed the vitamin A derivative, Accutane®.

Of particular note was a tender inflamed acne cyst on his left upper cheek. These cysts develop when bacteria, trapped by the closed pore, produce inflammatory changes with the accumulation of pus. When the plugged oil gland is unable to dump its product, it finally swells like a balloon until becoming so large that it bursts. A cyst forms when the body walls off the area damaged by irritating fatty acids coming from the sebum. We prescribed tetracycline, an antibiotic famous for its ability to kill the corynebacteria of acne.

When he returned three weeks later we were delighted to see no trace of the cyst on his left cheek. But now he had a new one up in the left

temple region. As we expressed disappointment that the tetracycline had not protected him from developing a new cyst, he said, "But that's the same bump, it never went away. It just crept up to where it is now." Now our disappointment turned to disbelief, as we had never seen an acne cyst creep around. We had seen them rupture and tunnel through the skin as sinuses, but, the original cyst always remained. What was going on? How could acne become a creeping eruption?

We decided to lance and drain his "new" cyst. On opening it we saw the answer. It contained a tightly coiled worm which proved to be the dog heartworm. These are round worms, nematodes of the genus *Dirofilaria*, which can produce subcutaneous abscesses in dogs, cats, and even raccoons. And they do migrate. The boy had a dog and we suspect the dog had heartworms. The mystery remains as to how the transmissible microfilariae got into this boy's skin. Usually, a mosquito bite transfers these larvae to the dog, but here we wonder if direct snuggling with the dog or possibly a flea bite was responsible for transfer to our patient.

Extracting the worm was the cure for this boy's creeping acne. Interestingly, he never posed a problem for his girlfriend or friends, because he was the end-stage host for dirofilariasis. This worm cannot reproduce in human skin and, therefore, cannot transfer from person to person.

This "creeping eruption" is to be contrasted with the true creeping eruptions due to larvae migrating through the skin. These are commonly seen on the feet and buttocks of children and adults at the seashore. Sand contaminated with infected dog or cat feces is the vector. This problem, known as cutaneous larva migrans, is usually due to the dog hookworm larvae, which always leave a visible trail, as they crawl through the dermis of the skin. In our patient the larva crawled deep into the subcutaneous tissue, and thus left no trace of its route.

QUESTIONS FOR THE DOCTOR:

- Have you ever seen an "acne cyst" that moves around?
- Does your patient have any close contact with animals, including dogs, cats, or raccoons?

- Does your patient ever go barefoot on a sandy beach or other area where there might be animal feces?
- Has your patient had a history of insect bites from mosquitoes, lice, fleas, ticks or flies?
- Has your patient ever traveled to tropical countries?
- Should you excise any skin lesion which moves around?
- Should your patient have a course of ivermectin, diethylcarbamazine, or thiabendazole to kill any other possible worms?

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OUR FIRST CASE

The chief complaint of a thirty-five-year-old man was that he was "in chains." Indeed, he had been brought in handcuffs and ankle chains to our clinic from the local jail. The officer's key freed the man's arm so the blue prison shirt could be slipped down to reveal the problem. There we saw on the outer side of his right arm a band of tense blisters, extending all the way from his shoulder to his hand. We deferred examining the rest of his skin in deference to the two anxious police officers.

This happened during the first month of a three year residency program when our diagnostic horizon was limited to what we had seen in the medical school clinics. However, we were proud of this, because each week of our senior year our professor of dermatology had demonstrated thirty patients, which our class could then examine at close range for the hour after the lecture. On graduating we knew more about diseases of the skin than any other organ.

We knew that the most common cause of the big blisters this man exhibited would be poison ivy dermatitis or sunburn. But the prison cell admitted very little sunlight and he could not have come in contact with poison ivy in the last few days. Could it be self-induced? Or, could it be a drug allergy? There was no evidence of a chemical or thermal burn and he had no access to drugs.

But surely, the location told us something. Yes, we decided, it must be a contact dermatitis. We asked if he slept on his right side. Yes, he did and without a shirt. The diagnosis became more apparent. He must be allergic to the mattress or to a disinfectant spray used on it. Our confidence mounted. Here was a skin disease due to some external contactant. Maybe

he was allergic to the cream the prison dispensary gave him. But no, that was used only after the blisters had appeared two days ago.

It was now checkout time with our Chief Resident, who came to the door. We presented him with the patient's history and our diagnosis of contact dermatitis, probably due to something in the mattress. There was a laugh from the resident who simply asked, "Does it hurt?" "Yeah, it sure does, doc." The resident spun on his heels and left, tossing the word "zoster" at me.

It was my first case of shingles and I will never forget it. "*If it is on one side and if it pains it is herpes zoster*." Since then we have seen dozens of cases of herpes zoster (shingles) on one side of the head, face, trunk, groin, or leg, but never again along the whole arm. Shingles is caused by chickenpox virus. This man had had, as all of us have had, chickenpox as a child. Our skin heals with or without scars, but the virus never leaves the infected nerve cells. Once this man's immunity dropped (possibly due to the stress of imprisonment) the virus came out of hiding in the ganglia of the sensory nerves. The patient first feels pain induced by the propagating virions, which then travel down the nerve to the skin where they induce blisters. His virus had traveled down the cervical nerves from the head and neck region. We have come through the years to have a more expanded view of shingles. It can come as blisters without pain and it can come as pain without blisters. We have learned that the sudden onset of unexplained unilateral pain calls for immediate specific antiviral therapy in the form of acyclovir (Zovirax®). Only in that way can the nerve damage be reduced and the agonies of postherpetic neuralgia be avoided.

Our lesson of that day in July: When you don't know anything, everything is a mystery.

And the corollary: The number of mysteries you see is inversely proportional to the number of things you know.

QUESTIONS FOR THE DOCTOR:

- Do the blisters hurt or itch?
- Does the linear distribution of the blisters follow a nerve distribution pattern?

- Are the blisters only on one side of the body?
- Could your patient have poison ivy dermatitis from brushing against a plant?
- Has your patient been weeding in the garden?
- Did your patient ever have chickenpox?
- Has your patient recently been exposed to anybody with chickenpox?
- Should your patient have a CBC, blood chemistry profile, UA, and chest x-ray to check for underlying health problems?
- Is your patient depressed, immunosuppressed, or short on sleep?
- Have you given your patient adequate treatment with acyclovir, famciclovir, or valacyclovir?
- Should your patient have oral or intramuscular steroids to help ease the pain and prevent postherpetic neuralgia?

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A STRANGE CASE OF ACNE

It was very strange how resistant a twenty-three-year-old woman's acne was to treatment. For months we watched one treatment after another fail. Her face continued to exhibit a full complement of blackheads, redness, and pustules at every visit. Local treatments achieved little, other than camouflage. A full array of systemic antibiotics staggered from the fray, accomplishing little more than inducing a yeast vaginitis. Even the acclaimed Accutane® failed, despite its advertising hype, "you've never seen results like this."

Was there a hormonal problem? No, her menses were normal and androgen, the prime mover of acne, was shown to be at low levels in her blood.

Was it genetic? No one in the family had had serious acne. Was it due to food imbalance? We had seen a case of terribly resistant acne in a Naval cadet who, disliking the Navy chow, ate nothing but Hershey bars. Could it be due to an intake of nuts, long known to us as a cause of postadolescent acne? No, her diet was balanced and a nut-free regimen had not had the slightest effect. Could it be due to a drug, such as dilantin? No, she was healthy and avoided all medications.

We explored her cosmetic history. No, she did not use occlusive greasy makeup which produces poral closure with subsequent acne. Nor did she use sunscreen lotions. Furthermore, she used no hair pomades. Her habits were obviously not the cause of her distress.

It was only after we focused on her work that we got a clue. Yes, we knew she worked for the state highway department. But it took detailed

questioning to learn that she often worked with the tar repaving crew. There she was a flagger, close to the hot rollers pressing a fine mist of tar into the air. Yes, she washed her face frequently. But the cure of her resistant acne came only after she started shampooing her hair every night instead of every morning, thus preventing her "dirty hair" from touching her face during sleep.

The tar mist had been the enemy we had not sighted. We had seen *McDonald's acne* in workers spending their days in the grease-filled air of the hamburger grill. We had seen *Mallorca acne* due to sun screen lotions used by vacationers to sunny islands. We had seen *theater acne* induced by heavy makeup used for the week-end performances of amateurs, a form of *acne cosmetica* from greasy makeup. We had also seen *car wax* acne in workers at car washes where wax sprays were used, and *halowax acne* from exposure to halogenated chemicals in industry.

But this was our first encounter with *asphalt acne*. The understanding of our patient's mystery came from following the rule: "Know thy patient."

QUESTIONS FOR THE DOCTOR:

- Did you take a family history of acne?
- Is your patient taking any medicines that could be causing acneiform lesions, such as corticosteroids, phenytoin, phenobarbital, or potassium iodide?
- Is your patient taking any hormones in the form of birth control pills or estrogen pills or patches?
- Is your patient an athlete who might be taking dietary supplements containing androstenedione or testosterone for enhanced athletic performance?
- Does your patient take growth hormones?
- Is your patient taking chasteberry, a hormone modulator, which may stimulate production of progesterone?
- Does your patient have breast cancer for which she is taking diethylstilbestrol or fluoxymesterone?
- Is your patient taking dactinomycin for treatment of a melanoma or sarcoma?

- Does your patient eat a diet rich in nuts, including walnuts, pecans, almonds, and macadamia nuts?
- Does your patient eat a lot of peanuts or peanut butter?
- Does your patient have psoriasis or seborrheic dermatitis of the scalp for which she uses a cortisone lotion?
- Does your patient's acne get worse mid-cycle or before her period?
- Could your patient have gram-negative folliculitis?
- Could your patient have *Pityrosporum* folliculitis?
- Does your patient eat large amounts of potato chips cooked in peanut oil?
- Does your patient drink large amounts of milk?
- Is constipation a chronic problem for your patient?
- Could your patient have steroid acne due to a triamcinolone inhaler?
- Is your patient taking danazol for treatment of endometriosis or fibrocystic breast disease?
- Does your patient have signs of hyperandrogenicity with hirsutism, alopecia, and irregular menses, suggestive of polycystic ovarian disease?
- Did you look in your patient's mouth searching for dental caries and infection?
- Does your patient use greasy makeup, sunscreens, or hair pomades?
- Is your patient under a lot of stress?
- Has your patient tried washing her hair at night instead of in the morning?
- Does your patient work on road construction with prolonged exposure to tar, asphalt, and diesel oil?
- Is your patient exposed to car wax or halogenated chemicals at work, which could cause chloracne?
- Does your patient work at McDonald's or some other fast food restaurant?
- Have you treated your patient with a wide variety of oral antibiotics, including minocycline, azithromycin, ampicillin, and cefuroxime axetil?

- Have you tried hormone treatment with oral contraceptives, prednisone, spironolactone, or tamoxifen?
- Have you prescribed topical antibiotics with erythromycin, tetracycline or clindamycin?
- Would your patient benefit from taking dapsone?
- Have you had your patient apply topical retinoids, including tretinoin and adapalene?
- Does your patient like topical medications with benzoyl peroxide or azelaic acid?
- Would your patient benefit from taking an oral antifungal agent, such as nystatin, ketoconazole, or itraconazole?
- Does your patient need oral isotretinoin (Accutane®) for severe acne?
- If you prescribe isotretinoin, have you done pregnancy tests and instructed your patient to follow mandatory birth control procedures?

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THE CASE OF THE GLASS EYE

"It's my right cheek. It burns and oozes," a twenty-eight-year-old woman told us. It had been that way for months. Cortisone had given some temporary help, but antibiotics were ineffectual.

What we saw was a weeping dermatitis extending downward from her right lower eyelid to the medial right cheek. The left cheek and her skin elsewhere were completely normal. Her past history was unremarkable, except for the loss of her right eye five years ago following an accident. The eye had been surgically enucleated and she wore a prosthesis.

We puzzled over the cause of her dermatitis, so localized to the right cheek. We eliminated the possibility of unilateral rosacea, because the eruption was too eczematous. Could she be allergic to a salve she was applying? We knew that some people even become allergic to the hydrocortisone in healing creams sold over the counter. A trial of complete avoidance of topical measures, soaps, and sprays had no effect. Could it be due to an underlying sinusitis of just that side? It seemed unlikely, because x-rays failed to reveal any sinusitis.

The most likely diagnosis was infectious eczematoid dermatitis, a condition in which chronic purulent drainage produces a band of acute dermatitis in the drainage area. We had seen it in patients with a chronic draining ear infection, in the form of an eczematous band on the face below the infected ear. Yes, our patient did have some drainage from the right eye socket, but it was not purulent. Infectious eczematoid dermatitis was a working diagnosis that was simply not working.

But we continued to suspect the right socket as the source of her problem. Removing the glass eye prosthesis was tried, to no avail. We then

reviewed the operation details and found that the surgeon had placed a gold ball in the space formerly occupied by the eyeball. This was done to prevent the artificial eye from appearing sunken, and also to improve the "eye" movement. Interestingly, gold has been used for centuries as a replacement eye. An ancient Hebrew reference cites a "golden eye" having been placed to improve a woman's appearance.

But, how could the gold implant in our patient's socket be the cause of her trouble? It seemed unlikely that she could be sensitive to gold, considering that gold rings are worn universally and harmlessly.

But it was the gold! We were astonished to see blisters form under a small square of pure gold leaf placed on her forehead for forty-eight hours as a patch test. She had such a strong allergic sensitivity to gold that tiny traces of gold molecules flowing down her cheek from the eye socket set off a severe reaction. It was as though she had a prosthesis made of poison ivy.

The cure came by having the gold implant removed and replaced by a plastic ball. It was a golden moment for all of us.

QUESTIONS FOR THE DOCTOR:

- Did you search for an underlying infection in the sinuses, teeth, eye socket, or ear, which could be causing infectious eczematoid dermatitis?
- Is there any drainage in the area?
- Did you take a detailed history for possible allergic contact dermatitis?
- Does something rub the affected area, such as clothing or bedding?
- Did you have your patient bring in all soaps, cosmetics, shampoos, and topical medications applied to the vicinity of the dermatitis so that you could inspect the ingredients for allergens?
- Did you do patch tests for possible contact allergens?
- Could your patient have unilateral rosacea?

- Could the patient have poor circulation in the affected area?
- Did you have your patient avoid applying all topical preparations to the affected area?
- Did you remove the prosthesis and examine the eye socket?
- Did you contact the surgeon for details of the original operation, searching for implants?
- Did you do a patch test for gold or other metals in the implant?
- Did you insist that the surgeon remove the offending implant?

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THE HAND ECZEMA CAPER

"It's my hands, Doc. They've been itching and burning for the past month and they're driving me crazy," a thirty-eight-year-old woman complained. What we mainly saw were the rough red scaling backs of her hands. But on her palms we also saw some scattered pinpoint-sized deep blisters filled with fluid, the so-called vesicles. Her skin elsewhere was clear. She had no fungus infection of her feet.

She was a housewife and had just passed a complete physical examination with blood studies, trying to find out why her hands itched and were so inflamed.

It was another case of "round up the usual suspects," with the line up including contactants, drugs, and foods. There was no unusual exposure of her hands to solvents, detergents or disinfectants. She denied excessive handwashing, a compulsive behavior easily controlled with fluoxetine (Prozac®). She had no hobbies such as flower arranging, with exposure to chrysanthemums, primula, or tulip bulbs. Her problem was a straightforward eczema. We could elicit no medication as a cause. She did not have a photodermatitis, for other light-exposed areas were clear.

Much to her surprise, we focused on foods as a cause. We have seen many chronic hand eczemas due to food allergy – not just from contact, but from eating a particular food. Pork is one of the most common causes. "Ham sandwich" hand dermatitis is quite common and often unrecognized. We told her about our patient who experienced a severe flare of hand eczema while eating bean soup in a restaurant. He knew he was allergic to pork, but what he did not know was that a ham bone

was used in the bean soup stock. And we told her of the dentist whose hand eczema was due to coffee. It was so severe he might have to give up his dental practice. His addiction to coffee was so severe he had to challenge himself three separate times with coffee before he became a believer. We explained we must find the cause of her problem or it would go on for years. We firmly believe that the longer a patient has had an unexplained hand eruption, the more likely it is to be due to a food allergy. "But," she replied, truculently, "I have had this only a month." Nevertheless, we urged her to keep a food diary and watch for flares, which come within minutes to a few hours after eating the troublemaker food.

When we next saw her two weeks later, her hands were much worse, with open weeping areas. But she had the answer! She told us that after seeing us she had gone out to lunch with a friend. During the luncheon her hands suddenly began to itch and burn. She rubbed them so much that her friend said, "you should see a doctor." "I have." "And what did he say?" "He didn't know, but said maybe it was due to food." At which point the friend said, "Why, you just had a cherry 7•up to drink. Maybe it's that."

Our patient went home thinking that that idea was stupid, "But I will prove how dumb it is." She then drank an entire liter of cherry 7•up. The ensuing flare was so severe she couldn't sleep. She now required an injection of cortisone.

On testing with small oral challenges we found that our patient was sensitive only to cherry 7•up, not regular 7•up, Cherry Coke, or regular Coke. She left our office complaining, "It ought to be against the law to put that cherry flavor in drinks for the public."

In solving a mystery there is no such thing as too much help. We like to know what the patient thinks and what our nurse thinks. We recall a case of unexplained hair loss in one of our patients, solved by our nurse. By sheer happenstance she rode home on a bus with this woman and observed that she kept pulling hairs out of her scalp. We also like to know what the relatives think, what our colleagues think, and what the medical literature thinks.

And in this case, the answer came from what a friend of the patient thought!

QUESTIONS FOR THE DOCTOR:

- Which parts of the hands are most affected, the palms or dorsal surfaces?
- Are both hands involved, or only one?
- Does the patient have hyperhidrosis of the palms?
- Does the patient admit to excessive hand washing:
- Could sun exposure be causing breaking out on the dorsal hands?
- Did the patient have a sudden emotional shock or severe stress just prior to onset of the breaking out, suggestive of dyshidrotic eczema?
- Did you take a careful occupational history for contactants, including metals, rubber, and formaldehyde?
- Is your patient a gardener with exposure to chrysanthemums, primula, poison ivy, or tulip bulbs?
- Does your patient handle any pets or livestock?
- Is your patient atopic, with hay fever, hives, or asthma?
- Did you check your patient's feet for tinea pedis and onychomycosis?
- Did you do intradermal skin tests for candida and trichophytin sensitivity?
- Does your patient wear rubber gloves and do they aggravate the problem?
- Does your patient have any food allergies, which cause hives, angioedema, itching of the palms and soles, red ears, headache, nausea, or diarrhea?
- Is your patient allergic to metal jewelry, with positive patch tests to nickel or dichromate?
- Would your patient benefit from a low nickel diet?
- Has your patient kept a food and beverage diary, looking for possible trigger factors of itching?
- Has your patient tried an elimination diet, avoiding pork, eggs, nuts, coffee, and tomatoes, one by one?

- Does your patient get frequent sore throats and did you examine the mouth for enlarged tonsils, which could harbor chronic strep infection?
- Does the hand eczema flare premenstrually, suggestive of progesterone dermatitis?
- Have you instructed your patient in careful hand protection, including cotton gloves under rubber or plastic gloves while shampooing, washing dishes, and cutting fruits, meats, or vegetables?
- Have you examined the patient's whole skin for signs of atopic eczema, psoriasis, scabies, and candidiasis?
- Have you taken a careful history of the patient's hobbies, searching for contact with epoxy, varnish, exotic woods, and modeling clay?
- Is your patient exposed to irritants at work, such as solvents, detergents, chemicals or rough fabrics?
- Did you do standard scout tray patch tests on your patient?
- Is your patient a hairdresser who might be allergic to fragrances, hair dyes, nail polish, or permanent wave solution?
- Is your patient a housewife who might be allergic to chromates in detergents?
- Did you instruct your patient that reactions to foods usually occur within minutes to hours of ingesting the responsible food or drink?
- Did you take a careful history of beverages consumed, including milk, beer, diet drinks, fruit juices, colas, whiskey, coffee, and tea?
- Did you instruct the patient to ask her friends and relatives to watch for her possible food allergies?
- Does your patient need a skin biopsy to rule out mycosis fungoides?

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THE SORE THAT WOULD NEVER HEAL

"I've had this sore on my chin for twelve years. It never heals. Can you help?" asked a fifty-four-year-old man. Ordinarily, a sore that does not heal is a skin cancer. But, three skin biopsies taken of the sore never showed any evidence of cancer. Nor was there any evidence of a draining sinus from an infected tooth. In fact, he had had excellent dental care with annual x-rays of his teeth, all totally normal.

Here was a man in excellent health with a sore that waxed and waned, but never completely healed. We secured a fourth skin biopsy and did bacterial and fungal cultures. Again, there was no cancer or other definable skin disease, such as scarring lupus erythematosus. There were also no pathogenic bacteria present or any evidence of the actinomycetes which cause the chronic ulceration of actinomycosis. X-ray of the jaw showed no osteomyelitis or other bone change. Again, the biopsy showed only nonspecific inflammatory changes.

The sore was never itchy, but our patient readily admitted to picking at the spot, trying to remove the crusts and debris. Sometimes, he felt that underlying ingrown hairs were responsible. We wondered if his constant picking of the chin could be a compulsive tic. This proved not to be the case, as psychotropic drugs had no effect.

At the time of his first visit, the sore was an open ulcer about a quarter of an inch in diameter. The skin around it was thick and firm (indurated) with about an inch of depigmentation void of beard hair on the left side of his chin.

The chronicity of the sore suggested he might be suffering from a deficit in immunity. However, he was receiving no chemotherapy, and did not have AIDS, according to blood tests.

As his visits to our office extended over months, and then years, we explored the possibility that his urge to pick might be coming from the release of irritants from bacteria, such as staphylococci. We prescribed short trials of powerful oral antibiotics, which helped but were inevitably followed by relapse. Meanwhile, he kept trying numerous topical anti-infective and corticosteroid preparations locally.

Nothing helped. After treating him for three years we began to wonder if he was destined to have this sore for the rest of his life. Must we conclude he had idiopathic "pickitis"? The solitary sore continued to stare at us. His skin elsewhere was completely normal, with the glow of health.

Convinced that there had to be a reason for his constant picking, we doubled our efforts to find an underlying infected tooth, requesting special study of the molars beneath the sore. Again, the results were negative, not only with his usual dentist, but also with a second one. But six months later a third dentist finally found a hidden periapical abscess in the first molar on the left lower jaw. Although root canal therapy produced an immediate flare-up of his sore, complete healing had occurred within a few months.

It is now nine years since his endodontic therapy. He has had no reappearance of the sore or the desire to pick at his chin. Only a faint white scar remains on his chin to remind him of the fifteen-year struggle. We have concluded that his inapparent focal dental infection caused the "sore that would never heal."

We knew from the start that his lesion was self-induced, a so-called "factitial ulcer," made by the patient. However, unlike some cases, there was no secondary gain or psychiatric problem. The final answer was that his dental abscess was at the root of his fifteen-years of digging. His tooth abscess had somehow induced an uncontrollable urge to pick. On a reflex level he was trying to dig out the cause, but he just could not go deep enough.

. . . When it comes to orphan patients, they may give up on us, but we never give up on them.

QUESTIONS FOR THE DOCTOR:

- Have you taken multiple skin biopsies from different areas of the non-healing sore?
- Did you do bacterial, mycobacterial and fungal cultures of the skin biopsy tissue?
- Did you request special stains, including acid fast, PAS, and silver, on the tissue removed from the sore?
- Was there any purulent drainage from the sore that could be cultured?
- Does your patient admit to "picking" at the sore?
- Have you requested dental examinations and dental x-rays searching for a dental abscess and dental sinus under the chronic sore?
- Have you ruled out actinomycosis?
- Does the patient have any lymphadenopathy?
- Has your patient had a recent chest x-ray?
- Has your patient had an ANA?
- Could your patient have osteomyelitis underlying the sore, as revealed by x-ray?
- Have you prescribed anti-anxiety medications to stop a compulsive tic?
- Have you given your patient pimocide in an effort to heal the factitial ulcer?
- Has your patient had a CBC, VDRL, chemistry profile, and HIV test?
- Have you treated your patient with antibiotics to eliminate primary and secondary infection?
- Did you have your patient seek a second dental consultation and did you personally call the dentist about the problem?

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BLACK BLISTERS

"Doc, I want you to drain my blood blisters," was the request of a sixty-six-year-old man. He told us the "blisters" had been coming out for the past two months. He also told us that three or four months ago he had felt a lump over his left shoulder blade area. It was painless, but getting bigger.

When he slipped off his shirt we saw several hundred black bumps on his chest and back. They were not blood blisters, but hard pitch-black tumors generally ranging in size from a pinhead to a walnut. The largest one on the back was an irregular lobulated mass three inches in diameter. Only a few small lesions dotted his face and arms.

As we took his history the problem became more ominous. He had been a construction worker all his life, going shirtless in the summer months, with no attempt to use sunscreens. He was retired and lived alone, with no one to tell him that the mole on his back had begun to enlarge and turn black. His health had been good until recently, when he noted how easily he became short of breath and that his legs were becoming swollen.

Sadly, we had to tell him there were no blisters to drain. We explained that only by sampling his skin tumors and studying them under the microscope would we solve the mystery of his lesions. We told him we feared he had a very serious problem.

We secured a skin biopsy and while awaiting the results, obtained a chest x-ray. On the x-ray we saw the reason for his shortness of breath. Both lungs showed the shadows of death, metastatic tumors. And then

came the brain scan, with evidence of three more metastatic tumors. Finally, a CT scan of the abdomen showed a tumor mass in his left adrenal gland.

But it was from the skin biopsy that the definitive diagnosis came. He had malignant melanoma, the dreaded "black cancer" of the skin. We knew that it had spread not only in the skin, but also internally. It had metastasized with extreme rapidity via his lymphatics and blood vessels. Within weeks he had traveled from good health to death's door.

Here was a man awash with the risk factors of malignant melanoma. He was light complexioned, with blonde hair and blue eyes, and had had excessive sun exposure. There was, however, no family history of melanoma, which would have increased his risk tenfold. Tragically, he had ignored the mole on his back, possibly due to its hidden location or perhaps from a subconscious or conscious denial of disease. In any event, it proved to be a fatal flaw in his health care.

We gave him the grim news, along with his treatment options. He was already beyond any help from the surgeons and radiotherapists. Only chemotherapy or immunotherapy could give him a flickering candlelight of hope. We knew the National Institutes of Health had a promising new vaccine for treatment of melanoma, but when we called we found he was too old for their scientific evaluation study, being older than sixty-five. A mere year on his birth certificate eliminated his best chance. We explained that with or without treatment he could probably expect to live for only a few months. He elected to remain untreated and within a month was dead.

With the incidence of malignant melanoma reaching one in every 100 people, our patient's "blood blisters" reaffirmed the need for public awareness of the importance of good sun-sense: Avoid sunburn. Use sunscreens. But above all, the melanoma manhunt should be a lifelong pursuit. Moles that change must be exchanged for a scar as soon as possible. If our patient had done so, he probably would be alive today.

And so, upon solving this last and most malignant mystery, we bid you adieu, hoping to write another book or two.

QUESTIONS FOR THE DOCTOR:

- Does your patient have a history of sunburn, starting in childhood?
- Did your patient ever use sun protection in the form of a hat, clothing, or sunscreens?
- Does your patient have a family history of moles which have turned to cancer?
- Was your patient aware that one mole had been changing, becoming larger and darker and developing an irregular edge?
- Has your patient ever had a bleeding mole?
- Does your patient have fair skin, freckles, blue eyes, and red or blonde hair?
- Are there redheads in your patient's family?
- Is your patient of English or Irish descent?
- Is your practice equipped to see a patient immediately for evaluation of a "changing mole"?
- Have you ever participated in a skin cancer screening clinic?
- Has your patient had staging of the melanoma by Clark's level and Breslow thickness?
- Should your patient with a melanoma have a sentinel node biopsy?
- Are you aware of any research therapeutic protocols which might help your patient?
- If you or a member of your family developed metastatic melanoma, what would be your advice?
- Does your patient vacation in sunny parts of the world?
- Is your patient a candidate for chemotherapy, radiation therapy, or immunotherapy (possibly with DNCB)?
- Does your office staff know the ABCD's of melanoma: **A**symmetry, **B**order irregularity, **C**olor variation, and **D**iameter over 6 mm?
- Does your patient have a large number of nevi or a large congenital nevus?
- Does your patient have dysplastic nevi?

- Did you note in your record the exact colors, configuration, location, and lesion size, as well as any satellite lesions?
- Did you photograph the lesions?
- Does your patient have any palpable lymph nodes?
- Have you considered referral to a treatment center for i.v. administration of the new wonder drug for metastatic malignant melanoma, aidesleukin (Proleukin®)?

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