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Queen Anne, studio of John Closterman, oil on canvas (circa 1702); © National Portrait Gallery, London.

UNITED NATIONS SHALL COMBINE
TO DISTANT CLIMES THEIR SOUND COMBINE
THAT ANNE'S ACTIONS ARE DIVINE
AND THIS THE MOST IMPORTANT DAY!
THE DAY THAT GAVE GREAT ANNE BIRTH
WHO FIX'D A LASTING PEACE ON EARTH.

—G. F. Handel, "Ode for the Birthday
of Queen Anne", 1713 (1)

GEORGE THE THIRD
OUGHT NEVER TO HAVE OCCURRED.
ONE CAN ONLY WONDER
AT SO GROTESQUE A BLUNDER.

—E. C. Bentley, "George III", 1929 (2)

HEIRLESS IN LONDON

WERE IT NOT FOR THE antiphospholipid antibody syndrome, the United States might now have a National Health Service. That's my conclusion from finding direct links between the most prominent victim of the



American revolutionaries toppling the statue of British King George III (engraving; later coloration)/Private Collection/Photo © Tarker/The Bridgeman Art Library.

syndrome—Queen Anne—and current debates over Scotland’s imminent secession from England. This September, Scots will hold a plebiscite on whether to dissolve a partnership that has lasted since Queen Anne presided over the “Acts of Union” (1707) (3). As Simon Schama quipped (4), Anne saw to it that the United Kingdom, which “began as a hostile merger would end in a full partnership. . . .” But, that was three centuries ago, and the going is tougher these days. Scotland’s prime minister has had to reassure anxious voters that a future spinoff would retain its popular National Health Service. He’s also told them that Queen Elizabeth II would remain head of state in Scotland (as she has in Canada, Australia, and New Zealand). He then set Scottish Independence Day to commemorate the UK’s founding mother, Queen Anne (3).

The Queen, a childless widow, died in 1714, sickened by “gout, dropsy, hemorrhage and stroke” (5). If poor Anne had produced a Stuart heir, a National Health Service in the United States today might look a lot like those in Scotland, Canada, or Australia.

ROYALTY AND AUTOIMMUNITY

Queen Anne's life and the Stuart dynasty were undone by systemic lupus erythematosus (SLE) and its harsh companion, the antiphospholipid antibody syndrome, which produces bleeding, clotting, stroke, and obstetrical calamity (6). Anne and her husband, George Oldenburg, sweated out at least 17 pregnancies from 1684 to 1700 (**Table 1**): all but one resulted in miscarriages, stillbirths, or infant death (7). Anne's only surviving child, William, the last Stuart of Kensington Palace, died at age 11, after infantile seizures, childhood dyskinesias, and gross hydrocephalus, symptoms now recognized as those of neonatal lupus (8).

It's clear that Anne suffered from SLE, an autoimmune disease that chiefly afflicts women of child-bearing age and their newborns. The Queen's contemporaries describe four clinical features that add up to current criteria for the diagnosis: a blotchy, pitted face with a malar rash; recurrent polyarthritis; facial and leg edema; and repeated seizures, nosebleeds, and lethal stroke (9). Official portraits of Queen Anne show variable joint swellings, obvious facial edema, and the classic lupine rash. Add her obstetrical history, and we arrive at the diagnosis of the antiphospholipid antibody syndrome. The syndrome is often tagged "Hughes syndrome", after my colleague Graham R. V. Hughes, who described a patient in London with ailments similar to those of Queen Anne. His seminal 1983 article in the *British Medical Journal* sums up the problem: "Thrombosis, abortion, cerebral disease and the lupus anticoagulant" (10).

TABLE 1. *Children of Anne Stuart, Queen of Great Britain, and George Oldenburg, Prince of Denmark*^a

● Stillborn daughter 1 Oldenburg b. 12 May 1684, d. 12 May 1684
● Mary Oldenburg b. 2 Jun 1685, d. 8 Feb 1687
● Anne Sophia Oldenburg b. 12 May 1686, d. 2 Feb 1687
● Stillborn child 1 Oldenburg b. 21 Jan 1687, d. 21 Jan 1687
● Stillborn son 1 Oldenburg b. 22 Oct 1687, d. 22 Oct 1687
● Stillborn child 2 Oldenburg b. c Oct 1688, d. c Oct 1688 ¹
● William Henry Oldenburg, Duke of Gloucester, b. 24 Jul 1689, d. 30 Jul 1700
● Mary Oldenburg b. 14 Oct 1690, d. 14 Oct 1690
● George Oldenburg b. 17 Apr 1692, d. 17 Apr 1692
● Stillborn daughter 2 Oldenburg b. 23 Mar 1693, d. 23 Mar 1693
● Stillborn daughter 3 Oldenburg b. 21 Jan 1694, d. 21 Jan 1694
● Stillborn daughter 4 Oldenburg b. 17 Feb 1695, d. 17 Feb 1695
● Stillborn son 2 Oldenburg b. 25 Mar 1696, d. 25 Mar 1696
● Stillborn son 3 Oldenburg b. 25 Mar 1697, d. 25 Mar 1697
● Stillborn son 4 Oldenburg b. 10 Dec 1697, d. 10 Dec 1697
● Stillborn son 5 Oldenburg b. 15 Sep 1698, d. 15 Sep 1698
● Stillborn son 6 Oldenburg b. 25 Jan 1700, d. 25 Jan 1700

^aSee ref. (7).

Hughes syndrome, which can also occur in the absence of lupus, results from antibodies directed against anionic phospholipids (presenting as lamellar bilayers on cell surfaces) and/or an associated plasma protein (β -2 glycoprotein) (11–13). Closely related antibodies, i.e., Hughes's "lupus anticoagulant", inhibit the phospholipid-dependent coagulation of normal blood. Each of these autoantibodies can induce cascades of injury against self or any product of the womb. Recent, multicenter studies show that in pregnant patients with antiphospholipid antibodies, measurements of the lupus anticoagulant are the best predictor of adverse outcomes. Antibodies to cardiolipin or to β -2 glycoprotein, do not predict adverse pregnancy outcomes, unless the lupus anticoagulant is also present (14). Graham Hughes has earned his eponym: it's fitting that he directs a unit at St. Thomas' Hospital, down Royal Street and a bridge away from Westminster Abbey, where Queen Anne lies forever.

"A LASTING PEACE ON EARTH. . ."

Before the reign of Queen Anne (1702–1714), England was torn by religious and family spats that ranged in intensity somewhere between today's Sunni/Shiite conflicts and the family squabbles of the Cheney sisters. The House of Stuart regained power in 1660 after Cromwell's Puritan misadventures. Anne's uncle, Charles II, restored the monarchy, presided over Restoration comedy, and chartered the Royal Society (15). Chuck 2 (as American royalists have it) was a middling Protestant, and Anne was brought up as such. But, next in line came a very partisan Catholic, James II, who happened to be Anne's father. After a short 3 years in power, James was overthrown in 1683 by Anne's Protestant brother-in-law (and cousin) William III. It was called the "Glorious Revolution" of 1688 and resulted in permanent exclusion of any Catholic successor (15). William III became joint monarch with Anne's elder sister Mary II: we know the pair from that college down south. Mary II's official biography documents that "the marriage survived although all three of her pregnancies were stillborn" (16). Two sisters, 16 stillbirths, no heirs? Time for some genomics here (17)!

Then came the younger sister's turn: Queen Anne with her own stillbirths, her gout, dropsy, and seizures. But, these days, her reign is remembered less for disease than for peace and prosperity. The "War of the Spanish Succession" had broken out on both sides of the Atlantic the year before her coronation. It pitted the great powers—England, Austria, and Holland versus France and Spain—in battles from the Alps to the Canaries, from Jamaica to the Arctic. Handel's musical tribute (above) celebrated Anne's major achievement, the Treaty of Utrecht (1713). The treaty not only established a peace that would last to midcentury but also left Britain in possession of Newfoundland, Nova Scotia, the Hudson Bay Territory, and Gibraltar (15). Schama had it right—that full partnership of the U.K.

had become “the most powerful going concern in the world”.

Anne followed a path set by grandfather Charles II as custodian of arts, science, and the commonweal. She was a patron of Christopher Wren, knighted Isaac Newton in Cambridge, and appointed Jonathan Swift the dean of St. Patrick’s in Dublin. By proclaiming the “Statute of Anne” (1707) for the “*Encouragement of Learned Men to Compose and Write useful Books*”, she established the basis of copyright law in Anglophone countries (18). In the American colonies, which comprised her contented subjects, she is renowned in name and deed. That town in Chesapeake Bay, Annapolis, is named for her, (19) as are Cape Ann in Massachusetts and Fort Ann in Washington County, NY. She is remembered for a unique “Act of Denization” granted to Luis Gomez, a Jewish refugee from the Spanish Inquisition in 1705. The document allowed him to conduct business, own property, and live freely within the colonies. His mill in Marlboro, NY, is a tourist site today (20). Among her other acts, deeds, and grants that remain in the news are those 215 acres the Queen bestowed on Trinity Church in Manhattan in 1705. The church elders are debating what to do with the \$2 billion it’s worth today (21).

Not bad for 1 dozen years of Stuart-ship, and again, one wonders what a living heir would have meant.

“SO GROTESQUE A BLUNDER”

Trouble came when the Hessians followed the Stuarts. Worried over Anne’s afflicted womb, Parliament passed the “Act of Settlement” (1701), which assured a Protestant line of succession. The nearest skein of that line led to Hanau (Hanover) and the three Georges—no Graces, they—who ruled from 1714 to 1820 (22). George I, a Hessian, who barely spoke English, kept several mistresses; in return, his wife eloped with a Swedish count, who was killed and dumped in a river on George’s order. He then had his young son, George II, arrested for siding with his mother and excluded from public ceremonies. When his father died of a stroke on one of his frequent trips home to Hanover, George II assumed the British throne and—one generation after Anne’s “lasting peace”—took the country to war again. George II personally commanded British troops in the War of the Austrian Succession: truce *sans* peace was the result. Both George I and II faced repeated insurrections from Scots unhappy with Hessian authority. The issue was settled in 1745, when “Bonnie Prince Charlie” and his Highlanders were defeated by the Redcoats at Culloden (23). In 1751, after George II’s eldest son Frederick died suddenly of mysterious injuries (attributed to a tennis ball!), the crown passed to George III, grandson of the warrior (24).

George III assumed leadership of the British Empire in 1760 at age 22. The official website of the Crown states that he is best remembered for provoking American independence and for going mad (25). Alan

Bennett’s popular play and film, “The Madness of King George” (1994), revived the story of a nutty monarch, crazed by “variegate porphyria” (26). Modern analyses reject that diagnosis but not its symptoms: blindness, deafness, and madness—episodic bouts of which followed loss of the American colonies (27). When his Redcoats and Hessian mercenaries were defeated by the Americans, he declared a General Day of Fast in 1778—a gesture understood as pitiful at the time.

*First General Gage commenc’d the war in vain;
Next General Howe continued the campaign;
Then General Burgoyne took the field and; and last
Our forlorn hope depends on General Fast* (28).

Whether his madness was caused by, or was coincident with, loss of his American colonies remains in doubt. What is certain is that George III blundered into his American quagmire through economic miscalculation. The empire was going broke, thanks to the costs of those successional wars with France and Spain and expenses of the East India company that ran India for the crown (29). By the 1770s, at a time when there were no income taxes, the United Kingdom required £4 million (£500 million today) simply to service its debt. The answer was to tax items in demand among the more prosperous of American colonies. George had figured out a solution. In a letter of the early 1770s, he wrote, “While the Sugar Colonies [the Caribbean] added above three millions a year to the wealth of Britain, the Rice Colonies [South Carolina, etc.] near a million, and the Tobacco ones [Maryland, etc.] almost as much; those more to the north [Pennsylvania on up], so far from adding anything to our wealth as Colonies . . . rivaled us in many branches of our industry, and had actually deprived us of no inconsiderable share of the wealth we reaped by means of the others” (25).

The answer was clear: impose taxes on sugar, tea, and commercial transaction. The Brits were sure that those moneymaking rivals would return some of the “not inconsiderable wealth” in the form of taxes. The result of that miscalculation was the American Declaration in Philadelphia of July 4, 1776, which lists in detail a litany of “. . .the patient sufferance of these Colonies” and explains the “necessity which constrains them to alter their former Systems of Government”.

We do not know whether a legitimate heir of Queen Anne’s would have forestalled rebellion in Scotland or revolution in America, but I can imagine a placid Anne or regal Chuck on the throne, making sure that “*United nations shall combine, to make a lasting peace. . .*” on both sides of the Atlantic. Without those antiphospholipid antibodies tugging at Anne’s womb, the Georges might have remained in Hesse, and the United States would have a National Health Service, just like Scotland. [F]

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A Hollywood Mystery

The Untimely Death of Jean Harlow

Robert S. Pinals, MD* and Eve Golden, BA

The sudden, unexpected death of Jean Harlow in 1937 was one of the most shocking events to hit the entertainment world since Rudolph Valentino's demise 11 years earlier.¹⁻³ Jean Harlow was only 26 years old, had been a top star for 5 years, and seemed to be a healthy, active young woman with no previous illnesses. She appeared with Robert Taylor at President Roosevelt's Washington Birthday Ball in January. Her most recent film, the comedy *Personal Property*, had opened in March, and she was at work on a new film with frequent costar Clark Gable. She left the set with what seemed to be minor illness at the end of May and was dead by June 7. Actually, her illness probably started several months earlier, after a severe sunburn, and terminated with renal failure. This raises the possibility that systemic lupus erythematosus (SLE) may have been the underlying cause of her death.

Jean Harlow burst into film stardom in *Hell's Angels* (1930), showcased as a platinum-blond vamp, but she showed no discernable acting talent. Harlow was born Harlean Carpenter to upper-middle-class parents in Kansas City, MO, in 1911. Preparatory school and an early, brief marriage left her a teenaged divorcee and bit player in Los Angeles in 1928. Then came discovery and stardom, for which the untrained and sheltered Harlow was totally unprepared. After 2 years of inferior performances, her downward-spiraling career was rescued by Metro-Goldwyn-Mayer (MGM) and producer Paul Bern. Frank Capra had directed her in the light comedy *Platinum Blonde*, and Bern saw her potential. He convinced MGM to sign her and mold her into the bright comic star she was destined to become.

From 1932 until her death, Jean Harlow emerged a successful actress and a style icon, with her platinum hair, antennae eyebrows, and bias-cut satin gowns (Fig. 1). In such bawdy comedies as *Red-Headed Woman*, *Red Dust*, *Dinner at Eight*, and *Bombshell*, she delighted audiences with her self-mocking wit and snappy wisecracks. When the Production Code was passed in mid-1934, Jean Harlow's light was somewhat dimmed as she toned down her brassiness and returned her hair to its natural honey-blond. In 1936, she costarred with Spencer Tracy, William Powell, and Myrna Loy in one of the year's hit comedies, *Libeled Lady*, and that same year, she had her first successful dramatic role in *Wife vs. Secretary*, with Clark Gable and Myrna Loy.

During this time, the fan magazines were filled with stories of her mansion, her numerous pets, her sports (golf, swimming, tennis), and, most of all, her love life. She had married her MGM mentor, Paul Bern, in 1932. Within months, his common-law wife reappeared and Bern killed himself. Friends and coworkers

rallied around Jean, and she bounced back fairly quickly. She briefly married cinematographer Harold Rosson in 1934, and at the time of her death, she had been dating costar William Powell for 2 years.

ILLNESS AND DEATH

The time of onset of Harlow's fatal illness is far from clear. In late August or September 1936, after sunbathing on the beach, she had severe burns over her face, back, and extremities. Her lips were so swollen that speech was difficult, and her blistered skin was treated with boric and tannic acids. She took elixir of aleurate (a barbiturate) for pain. After the episode, she complained of severe fatigue and exhaustion. Two years previously, a physician had advised her to avoid the sun; the reason for this warning is unknown but may have been related only to her fair complexion.

In early February 1937, on a publicity tour, she and many others developed a severe "flu," which included nausea and abdominal cramps.

A month later, she visited her dentist, with complaints of pain on brushing her teeth and was found to have gingival infection. The dentist recommended extraction of her 4 wisdom teeth, because of impaction and infection, and suggested that this could be accomplished in 4 office visits. However, Harlow's mother did not approve of this approach and demanded that the procedures be done at the Good Samaritan Hospital in late March under general anesthesia. One of Harlow's biographers noted that the extractions were performed by a plastic surgeon and ophthalmologist, perhaps because there was no dentist on the hospital staff.² After 3 extractions, she "lost a heartbeat," and the operation was terminated. A friend reported that she had almost died.² She remained in the hospital for 18 days and looked "bloated" on



FIGURE 1. Jean Harlow on set of *Dinner at Eight*, 1933 (courtesy of Eve Golden).

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discharge according to Hollywood columnist Louella Parsons. She appeared to be in radiant good health on the cover of *Life* magazine on May 3, but the photograph had been taken 2 years earlier.

In May, while shooting her last movie, *Saratoga*, in which she costarred with Clark Gable, she was anorexic but, nevertheless, gaining weight. Her eyes were red and swollen, and she was sweating excessively. She also had intermittent abdominal pain and vomiting, which her physician attributed to complications of her recent “flu” and a mild gallbladder inflammation. On May 27, she left the movie set complaining of a toothache and abdominal pain. She appeared to be pale and bloated. On May 30, she had chills, fever, and nausea and was unable to eat or drink. Her physician, Dr Ernest Fishbaugh, examined her the following day and ordered blood and urine tests and around-the-clock nurses.²

On June 2, she had more intense abdominal pain, vomiting, and intermittent delirium. She had been receiving intravenous dextrose and “sulfa drugs.” Her body was diffusely swollen, and her breath smelled of urine. Dr Leland Chapman, the junior partner of her primary physician, was called and noted that her blood urea level was high. His diagnosis was “acute nephritis,” and he suggested that she had received too much fluid intravenously and now should have diuretics. What additional treatment was given is unknown, but her condition continued to worsen. On June 6, she was taken by ambulance to the Good Samaritan Hospital and received 2 blood transfusions and additional intravenous fluids, but on the following morning, there was more swelling of her face and scalp and Dr. Chapman considered “drilling holes in her temples” to release the fluid. She was also found to have swelling of the pericardium¹ and later became increasingly incoherent and then comatose. The Fire Department was called to administer oxygen using their emergency resuscitation equipment, but to no avail. She was pronounced dead on June 7, 1937, at 11:28 a.m. The death certificate noted the causes of death to be acute respiratory infection, acute nephritis, and uremia.⁵ There was no autopsy.

AFTERMATH

Despite the family's request that there be no public display, large crowds gathered at Forest Lawn Church to glimpse Hollywood royalty attending the formal service. Jean Harlow was one of the best liked people in show business. Her co-workers called her “The Baby,” and she became a sisterly pal to such leading men as Clark Gable, Spencer Tracy, Robert Taylor, and Walter Pidgeon.

Even female competitors liked her—Myrna Loy, Carole Lombard, Marlene Dietrich, and Marion Davies, all counted her as a close friend.

The film she was working on when she died had been nearly completed; 3 doubles were used for long shots, close-ups (turned away from the camera or hiding behind hats), and voice over. *Saratoga* was not one of Harlow's better films, but morbid fascination made it a hit. Jean Harlow's death caused other ripples in Hollywood; she was to star in *Topper* and was replaced by Constance Bennett; a loan-out arrangement with 20th Century Fox fell through as well. Harlow would have appeared in *In Old Chicago*, and Shirley Temple loaned to MGM for *The Wizard of Oz*; instead, MGM had to settle for studio contract player Judy Garland.

DISCUSSION

The fragmentary details of Harlow's final illness suggest that she died with uremia from acute renal failure. Several preceding events may have been factors contributing to the out-

come. About 10 weeks before her death while undergoing dental extractions under general anesthesia, she may have had a cardiac arrest or arrhythmia. Fluid retention and weight gain occurred later despite a poor appetite, diminished fluid intake, and excessive sweating. Gingival and respiratory infections were present, but she may also have had infection elsewhere. Abdominal pain and vomiting, later accompanied by chills and fever, were attributed to cholecystitis by her physicians, but this was a clinical diagnosis. Gallbladder imaging (cholecystography) was available in 1937, but it would have been performed during a hospital admission. Many alternative causes for her gastrointestinal symptoms include pancreatitis and enteric infection. She was probably treated with a sulfonamide and possibly a mercurial diuretic, both of which may cause renal injury or dysfunction.

A great deal of important information is missing, including her physical findings, urinary output, blood pressure, time of onset of azotemia and its rate of progression, and results of urinalysis and other tests. Presumably, she had significant anemia because blood transfusions were administered. Her massive fluid retention in the face of poor intake suggests that she was oliguric. Serum sodium and potassium were not measurable in 1937, but hyperkalemia from renal failure and hyponatremia from dextrose infusions may have contributed to her demise.

Sulfanilamide was marketed in the United States by several pharmaceutical companies in 1936 but was highly soluble and seldom responsible for crystalluria and renal tubular obstruction.⁶ Second-generation sulfonamides, with broader spectra of antibacterial activity, were not available until 1938; these were much less soluble and required high urine volumes and alkalization to avoid obstructive uropathy from crystal precipitation.⁶ During September and October 1937, 3 or 4 months after Harlow's death, at least 73 patients died after taking “elixir sulfanilamide,” including several in California.⁷ Federal authorities traced the cause to diethylene glycol, which had been used as a solvent. No human or animal studies for safety or efficacy had been performed before marketing this elixir. The patients were ill for 7 to 21 days with anuria, abdominal pain, nausea, vomiting, and stupor. No details about Harlow's treatment with a sulfonamide are known, but it would seem that the “elixir” was not available before her death.

Harlow's physician announced his intention to treat her with diuretics 5 days before her death, but we have no specific information on which medication was given if any. The most effective and widely used diuretics in the 1930s were organic mercurials. These had been used to treat syphilis and, in 1919, were noted to cause a dramatic diuresis.⁸ By 1927, less toxic mercurials were available and were administered parenterally.⁹ However, they were shown to cause renal tubular necrosis in some cases, and their use in patients with renal failure was controversial.

Did Harlow have an underlying kidney disease that was aggravated by the factors cited above? Harlow's death certificate identified “acute nephritis” as the cause of her renal failure. The nonspecific term might include many types of glomerular and interstitial nephritis recognized today. Without additional information, it is difficult to suggest which would be most likely. In view of her age and sex, SLE may be a likely cause of acute nephritis in Harlow's case. Most practicing physicians were unfamiliar with SLE in 1937. It was recognized by a few academic internists and dermatologists as a rare and often fatal disease of young women; the diagnosis was usually confirmed at autopsy because a diagnostic blood test would not be available until 1948.¹⁰ Systemic lupus erythematosus was not even mentioned in 2 of the most popular contemporary textbooks of medicine^{11,12} or in a textbook of rheumatology.¹³

Osler¹⁴ described the visceral manifestations of this rare skin condition in 1904 in 19 patients, but none of his fatal cases had postmortem examinations. The 1924 report of verrucous endocarditis in 4 autopsied patients attracted considerable attention and resulted in the use of the eponym “Libman-Sacks disease” for SLE during the next 25 years. Only 2 of these patients had a typical lupus rash and 3 had nephritis.¹⁵ The concept that SLE might occur without skin lesions was not pointed out until 1936¹⁶ and not widely accepted until the 1940s. Nephritis confirmed at autopsy was described in 18 of 23 SLE patients by Baehr et al.¹⁷ in 1935. They described the “wire loop” thickening of glomerular capillaries as a special feature of lupus nephritis.

Did Harlow have SLE? She had a severe sunburn about 9 months before her death, followed by prolonged, severe fatigue, and fluid retention. Other features of SLE were identified later, including anemia and a pericardial effusion, but both could have been related to renal failure, and fever, which could have been due to infection. Her abdominal pain could be attributed to serositis, but there are many alternative explanations. If the pericarditis produced cardiac tamponade, hepatic congestion could cause abdominal pain and other gastrointestinal symptoms.

In summary, Jean Harlow's death remains a mystery, and many explanations are possible, but one is tempted to suggest the following highly speculative scenario: (1) onset of acute lupus nephritis after a severe sunburn, (2) superimposed ischemic renal injury during surgery, (3) additional drug-induced injury by sulfonamides or organic mercurials, and (4) other factors including sepsis and electrolyte disturbances contributing to decompensation and death.

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Lupus in the Mid-20th Century

The Life and Death of Flannery O'Connor

Robert S. Pinals, MD

Among American fiction writers, Flannery O'Connor has always been a marvelous anomaly.¹⁻³ Since her death in 1964, her reputation has continued to grow, despite the limited volume of her work (2 short novels and 19 stories) and its quirky, provincial subject matter.^{4,5} She wrote about life in rural Georgia, where she spent most of her adult years, almost as an outsider. She was a devout Catholic in an evangelical Protestant world, an unmarried woman living in her mother's family farm, and a closet intellectual among her rustic neighbors. Yet, from this limiting experience, she imagined characters of enduring interest and complexity, in stories that combined themes of violence, comedy, and spirituality.

Flannery O'Connor developed systemic lupus erythematosus (SLE) in 1950, a time when most physicians were just becoming aware of this seemingly rare and generally fatal condition, because of the recent discoveries of a diagnostic test⁶ and an effective treatment.⁷ Most of the details of her illness, and her remarkable efforts to overcome its devastating consequences, are derived from her letters.⁵ A previous report of her case, dealing mainly with her personal struggle to cope with SLE, was published in 2003.⁸

ILLNESS AND DEATH

When she graduated from Georgia State College for Women in 1945, Flannery O'Connor had already decided that she would be a writer. She attended writers' workshops in Iowa and upstate New York, forming relationships that would sustain her for the next 2 decades.

Her first significant health problem occurred in December 1949 (age 24 years) when she returned to her home in Milledgeville, GA, for a holiday visit. She became seriously ill, but there was no description of her symptoms. Surgery was performed to correct a "floating kidney," and she was hospitalized for a month thereafter.⁵

In December 1950, while retyping the manuscript for her first novel, *Wise Blood*, she developed heaviness and aching in both arms. She was examined by a physician in Connecticut, where she was staying with friends, and told that she probably had rheumatoid arthritis. Further studies were recommended upon her return to Georgia for the holidays. Her symptoms, now including fever, worsened during the train trip, and she was hospitalized immediately upon arrival by her family physician, an internist. She was treated with a new "miracle drug," cortisone, with improvement in pain, but continued to have a high fever. Presumably there were laboratory results suggesting

kidney involvement, because her physician called Dr Arthur Merrill, Georgia's first nephrologist. Merrill felt that the picture was compatible with SLE; he suggested that she should be transferred to Emory University Hospital, and this was accomplished in January 1951. Letters several years later suggest that she may have had a typical facial rash early in her illness. She was found to have a positive lupus erythematosus cell test and received 10 transfusions for anemia. She was placed on a strict low-salt diet, and cortisone was eventually replaced with adrenocorticotrophic hormone (ACTH) injections 4 times a day. The frequency of injections was reduced, and she was discharged after a month on ACTH once daily.

In June 1951, she was well enough to return to her friends, the Fitzgeralds, in Connecticut. She learned from them that her diagnosis was SLE; her mother had asked her physicians to withhold this information for fear that the deadly prognosis would be too dispiriting. O'Connor was familiar with "lupus." Her father had died of this disease in 1941 at age 45 years, only 4 years after it first appeared as a discoid patch on his forehead.

In July 1951, she developed fever and other symptoms suggesting a viral illness. Dr Merrill gave her 2 transfusions and increased her ACTH dose. In January 1953, she wrote, "I am doing fairly well these days, though I am practically bald-headed on top and have a watermelon face," suggesting that she had significant alopecia and cushingoid features.

In early 1954, she developed a limp and was told that she had "rheumatism" in the hip. In 1955, she substituted the "newest wonder drug, Meticorten" (prednisone) for ACTH and was able to add salt to her diet. However, her hip pain had progressed, and she required crutches. X-rays later showed "softening of the top of the leg bones due to failure of the circulation to the hip." This condition, aseptic or avascular necrosis, resulted in progressive pain and disability. She was hospitalized late in 1960 at Piedmont Hospital in Atlanta for further studies. O'Connor wrote to a friend: "My last x-rays were very bad, and it appears the jaw is going the same way as the hip is. I had noticed a marked change in the position of my mouth." Two days later, she wrote to another friend, "What they found out at the hospital is that my bone disintegration is being caused by the steroid drugs which I have been taking for 10 years.... So they are going to try to withdraw the steroids...." Her SLE had been clinically inactive during this interval, and apparently, this was confirmed by laboratory studies. Dr Merrill probably referred to O'Connor's case in an editorial⁹ in 1961 on the use of steroids in renal disease; he described an SLE patient on prednisone 4 to 6 mg/d for 9 years, who developed bilateral aseptic necrosis of the femoral heads after 6 years and of the mandibular condyles after 8 years. Apparently, steroids were tapered during the first half of 1961. In May, she was taking chloroquine and mentioned that steroid injections in both hips a month previously had produced benefit for only 2 weeks. Hip surgery was under consideration, but 2 orthopedic consultants had conflicting opinions.

After steroid withdrawal, O'Connor's correspondence mentioned no new health problems, until Christmas day in 1963,

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when she reported to a friend that she had fainted several days earlier and was restricted to bed. She was found to be anemic, apparently due to vaginal bleeding, thought to be caused by a fibroid tumor. On February 25, 1964, she was hospitalized in Milledgeville for a hysterectomy. Dr Merrill had been concerned that surgery might provoke a flare-up of SLE and expressed a preference for performing the operation in Atlanta. The procedure appeared to be successful, and she received intravenous steroids for 3 days postoperatively. She returned home on March 5, but developed cystitis 2 weeks later and wrote to a friend on March 28, "I suspect it has kicked up the lupus again. Anyway, I am full of infection and am back on the steroids."

She returned to the hospital for 10 days the third week in April because "...I woke up covered from head to foot with the lupus rash." In late May, she was admitted to Piedmont Hospital in Atlanta for anemia, weakness, and a 20-lb weight loss. Her blood pressure was "dangerously" high. She was placed on a low-protein diet, suggesting that she was azotemic, and received 4 transfusions because her hemoglobin was "down to 8." After almost a month, she was discharged home. She was growing weary of the hospital, and there were hints that her insurance was running out. "My dose of prednisone has been cut in half on Dr Merrill's orders because the nitrogen content of the blood has increased by a third." In late July, she received another transfusion and "a double dose of antibiotic for the kidney... and they are withdrawing the cortisone." However, soon afterward, she became critically ill and was rushed to the local hospital. She lapsed into coma and died on August 3, 1964. She was 39 years old. In her letters, she frequently expressed distress over her appearance, with moon face and alopecia. During the summer, she had finished rewriting her last story, *Judgement Day*. The last line was: "Now she rests well at night, and her good looks have mostly returned."

DISCUSSION

In late 1950, Flannery O'Connor had onset of arthralgia, myalgia, fever, and facial rash. She was hospitalized and found to have severe anemia, abnormalities on urinalysis, and a positive lupus erythematosus cell test. The latter⁶ had been described in 1948 and was available in most academic hospitals in 1950. The use of cortisone and ACTH to control symptoms⁷ of SLE had been described earlier in 1950, and she responded well to what was then considered to be a high dose of cortisone (150–250 mg/d, equivalent to 30–50 mg/d of prednisone). No details of her nephropathy are available, but it was recognized that this did not improve as dramatically as other SLE manifestations.⁷

One might speculate about the possibility that her "serious illness" requiring hospitalization a year earlier might have represented the onset of SLE. The diagnosis of "floating kidney" (nephroptosis) was frequently proposed as an explanation for pain in the back, abdomen, groin, or flank and treated surgically (nephropexy) in the early 20th century.¹⁰ In the absence of details of the illness, this question cannot be resolved. However, lupus nephritis is usually not a source of pain.

Multiple blood transfusions were given, suggesting that she had significant anemia, which may have been hemolytic. Symptoms of SLE were controlled on ACTH, but she became aware of cushingoid features after the first year. During the third year of her illness, O'Connor developed progressive hip pain, which was later attributed to avascular necrosis (AVN). This would be the main source of disability for the remainder of her life.

Avascular necrosis or osteonecrosis was first reported in SLE in 1960,¹¹ but O'Connor experienced hip pain several years before this report, with radiographic confirmation of the diagnosis in 1955. High-dose corticosteroid therapy has been recognized as the most important risk factor,¹² and more recent magnetic resonance imaging studies have shown that AVN, which is often asymptomatic, may start within a few months after initiation of corticosteroids.¹³

After 8 years of treatment, she noticed painless misalignment of her mandible, which was found to be due to AVN of the condyles; this is a rare site for steroid-induced AVN.¹⁴ The progressive course of AVN is not altered by reduction or withdrawal of steroids, but this was not appreciated in 1961. O'Connor's low-dose prednisone was tapered and withdrawn, and treatment with chloroquine was initiated. This seemed reasonable because her SLE appeared to be inactive.

Systemic lupus erythematosus did not recur for about 3 years after steroid withdrawal and was provoked by a hysterectomy. The exacerbation included anemia, rash, hypertension, and azotemia, with superimposed urinary tract infection. Reintroduction of steroids did not alter her fatal progression. Hemodialysis was available in 1964, but reports of its use in end-stage lupus nephritis were limited.¹⁵

Even without life-extending measures such as dialysis, O'Connor's survival exceeded expectations. She lived for 14 years after onset of SLE. A 1964 report of a large series of SLE patients, many of whom did not have renal involvement, found that only half were alive after 10 years.¹⁶ An earlier 1955 report, reflecting survival in the precorticosteroid era, found only half were alive after 4 years.¹⁷ O'Connor's excellent medical care may partially explain her longevity, but her personal qualities and lifestyle were probably even more important.

O'Connor coped with her illness by obsessive adherence to a daily routine, which gave the highest priority to her literary productivity. Her energy level was highest in the morning; she attributed this to steroid therapy. "Cortisone makes you think night and day until I suppose the mind dies of exhaustion"³ After the 7 a.m. morning mass, she wrote for 3 hours. Afternoon activities started with gardening (always wearing a broad-brimmed hat to shield her face from the sun). She tended to her chickens and other more exotic fowl, in which she had a lifelong interest. She had first come to brief national attention in the Pathe Movietone News as the 5-year-old Georgia girl who had taught a chicken to walk backward. Later in the day, she would read and correspond with friends and literary colleagues. From time to time, she received visitors. One of her biographers estimated that she made about 60 trips to give lectures or readings from her works in other cities, primarily at colleges and universities.³ During most of her years with SLE, O'Connor walked with crutches, but was functionally independent despite this handicap. Her bedroom was on the first floor, and she had few stairs to climb. She managed to travel alone by train or plane. She seldom complained or talked about her illness and regarded it as an obstacle to overcome and an opportunity for spiritual growth.

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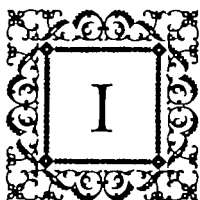
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The History of the Disease Called Lupus

BRIAN POTTER

INTRODUCTION



IN antiquity the Latin word for crab, *cancer*, was used for corroding ulcerations generally. The swollen veins surrounding some tumors resemble crab limbs. As early as the fourteenth century the Latin word for wolf, *lupus*, was another medical term for an ulcerous disease. While cancer could involve any tissue of the body, lupus always referred to a disease of the skin. Around 1400 Lanfranc mentioned that some termed such conditions *lupus*, others *cancer*. In 1590 Barrough used *lupus* to refer to "a malignant ulcer quickly consuming the neather parts." In the latter part of the seventeenth century Blancard in his *A Physical Dictionary* defined *lupus* as "a sort of Canker in the Thighs and Legs."¹

Paracelsus in the sixteenth century and others in the seventeenth century compared these ulcers to a hungry wolf eating the flesh. He thought that the lupus was devouring tissue with a greater blood supply, which became his rationale for treatment by blood-letting. Other physicians applied a small piece of hen's flesh to the ulcer, thinking that consumption of the meat would show that the lupus was still active.

After the seventeenth century some medical writers began to refer to lupus in the differential diagnosis of ulcers of the nose and face. Johannes Soleus is said to have employed the term in this way about 1710.²

During the same period—late medieval times through the seventeenth century—ulcers of the face were known as *noli me tangere* (touch me not). As early as 1398, in John of Trevisa's translation of Bartholomeus

1. *The Compact Edition of the Oxford English Dictionary*, 3 vols. (Oxford: Oxford University Press, 1971–87), I, 1679.

2. H. E. Michelson, "The history of lupus vulgaris," *J. Invest. Dermatol.*, 1946, 7, 261–67.

Anglicus' *De Proprietatibus Rerum*, this term was used to refer to a cankerous postume (abscess) in the face. In 1527 it was described as an evil sore; in 1577 as an ulcer taking root at the gristles of the nose; and in 1601 as an ill-favored lesion in the nostrils. In 1834 it could be said that "the terms lupus and noli me tangere are synonyms in British medicine, and have always signified the same thing since they have been used in any definite sense."³

Willan and Bateman effectively standardized the medical word lupus early in the nineteenth century, referring to a nodular eruption sometimes progressing to ulceration and often seen on the face. Willan described lupus in his work on cutaneous diseases, and Bateman recorded Willan's teachings in his own synopsis. The common, consuming and ulcerating lupus was then called variously lupus willani, vulgaris, tumidus, hypertrophicus, or exedens.⁴

Another chronic red eruption was known as centrifugal erythema, erythema perstans, seborrhea congestiva, and erythema atrophicans. The French dermatologist Cazenave in 1851 was the first to regard this as a variety of lupus. He named the disease *lupus érythémateux*, the first qualification of the term with the word "erythematous."⁵

Cazenave described the redness, the thinning of skin without ulceration, and the varied appearances of the lesions. The disease could manifest itself as urticarial on the face or chilblain of the nose, and occurred particularly in women. They were usually in otherwise excellent health, but the lesions resulted in indelible cicatrices. Although lupus generally appeared in adolescence, the erythematous disease developed more often in middle life. This less common, discoid, localized, atrophic but non-ulcerating type was thereafter called lupus erythematoses, sebaceus, or nonexedens.

Physicians were unaware that lupus vulgaris, scrofula, miliary disease, and caseous pneumonia had a common etiology. After the discovery of the tubercle bacillus by Robert Koch in 1882, the tubercular cause of all these diseases became known. Lupus vulgaris was then sometimes called tuberculosis luposa cutis, or surgical tuberculosis, excision being the optimal treatment in some cases. Hilliard's lupus miliaris disseminatus

3. (n. 1) *Compact Oxford English Dictionary*, I, 1935.

4. John Thorne Crissey and Lawrence Charles Parish, *The Dermatology and Syphilology of the Nineteenth Century* (New York: Praeger, 1981), p. 26.

5. Alphée Cazenave, "Lupus érythémateux (Érythème centrifuge)," *Ann. Mal. Peau*, 1851, 3, 297. Trans. in W. B. Shelley and J. T. Crissey, *Classics in Clinical Dermatology* (Springfield: Charles C Thomas, 1953), pp. 65-69.

faciei also came to be considered tubercular. Bernier's lupus pernio, however, was found to correspond to a different disease still of unknown cause, namely sarcoidosis.

Even when the tubercular nature of lupus vulgaris and lupus miliaris disseminatus faciei was established, this did not prove that lupus erythematosus was not of tubercular etiology. In 1891 Hallopeau presented a case of the rare exanthematic form of lupus erythematosus to the French Society of Dermatology. Besnier, Wickham, and others still considered it to be of a tubercular nature.⁶ The disease often occurred coincidentally with pulmonary tuberculosis until effective therapy for this infection became available many years later.

In 1897, in Allbutt's *A System of Medicine*, Simon and Williams mentioned the treatment by tuberculin of lupus of the nose, and Anderson listed tuberculin among the possible treatment measures for lupus vulgaris, commenting that its results were not as favorable as had once been expected.⁷ This treatment sometimes led to disastrous results when the case was actually one of lupus erythematosus. A patient with diffuse lupus erythematosus unfortunately treated with tuberculin was recorded as late as 1915.

Until the last decade of the nineteenth century, the observed curative value of sunlight in some diseases was attributed to its physical or thermal action. Finsen discovered that the ultraviolet rays were responsible for the bactericidal properties of sunlight. He published in 1896 his work on the employment in medicine of these actinic rays. The following year, after further experimental work, Finsen published another paper on the treatment of lupus vulgaris by ultraviolet light rays.

Finsen, Hagemann, and Jorgensen founded the Light Institute in Copenhagen in 1896. It had the capacity of treating 200 patients daily by the Finsen carbon-arc lamp, which produced chiefly blue, violet, and ultraviolet light. The Institute treated a total of over 2000 patients suffering from non-pulmonary tuberculosis, rickets, and probably other diseases. The cure rate was sufficiently impressive that, as a result of this work, Finsen was awarded the Nobel Prize for Physiology or Medicine in 1903.⁸

Ultraviolet rays were also known as chemical rays, perhaps because

6. Louis Wickham, "Letter from Paris," *Br. J. Dermatol.*, 1892, 4, 123-27.

7. Thomas Clifford Allbutt, ed., *A System of Medicine*, 8 vols. (New York: Macmillan, 1897), 4, 685 and 8, 795.

8. *Encyclopaedia Britannica*, 24 vols. (Chicago: Encyclopaedia Britannica, Inc., 1954), 9, 259-260.

one of the effects of this treatment was to raise the level of calcium circulating in the blood. Even a highly nutritional diet could produce strikingly beneficial effects in patients with lupus vulgaris. Gerson, Hermansdorfer, and Sauerbruch devised a low carbohydrate diet, salt free and rich in protein, supported by cod liver oil and calcium supplements. On this basis, the administration of vitamin D in massive doses later revolutionized the treatment of lupus vulgaris. Calciferol is the trade name for ergocalciferol, still available and listed in the United States Pharmacopeia. The high doses required to treat lupus vulgaris, however, can induce toxic effects.⁹

The discovery of streptomycin in the 1940s led to the first antibiotic treatment for all forms of tuberculosis, including lupus vulgaris. The synthetic drug para-aminosalicylic acid was introduced soon after, and eventually isoniazid, ethambutol, and rifampin were synthesized. Conventional therapy until recently was a course of isoniazid and ethambutol for as long as two years. In the last decade of the twentieth century the current treatment for most forms of tuberculosis is a nine-month course of isoniazid and rifampin.

With modern therapy, the incidence of tuberculosis was greatly reduced. It became obvious that this infection bore no relation to lupus erythematosus. Now, in the era of the human immunodeficiency virus, tuberculosis case rates have again increased substantially. Epidemics of multiple resistant disease have occurred in several parts of the United States.

Lupus vulgaris was human tuberculosis in its cutaneous focus, while scrofula usually represented bovine tuberculosis acquired by drinking unpasteurized, infected milk. Effective antitubercular therapy has almost vanquished both of these mycobacterial diseases from Western societies. Atypical mycobacterial infections are now increasing in frequency, or are recognized more often. They are caused by photochromogens and scotochromogens that do not respond to most antitubercular drugs and have now partly replaced the erstwhile cutaneous tuberculosis.

THE CONCEPT OF CONNECTIVE TISSUE DISEASE

Kaposi first recognized a systemic disease accompanying the eruption of lupus as a definite syndrome in 1872. He called the disease "lupus

9. George Clinton Andrews, *Diseases of the Skin*, 2nd ed. (Philadelphia: W. B. Saunders, 1938), pp. 361-62.

erythematosus disseminatus" and established its relationship to discoid or fixed lupus. Kaposi realized that the disease may appear as a severe, generalized, febrile, acute or subacute eruption with intense constitutional symptoms. It was most alarming that some cases were lethal, characteristically in young women.¹⁰

In 1889 and 1892 Hardaway described two more cases of lupus erythematosus with lethal complications. Sporadic individual fatal cases of lupus continued to be recorded. It remained a mystery as to why some patients died of the disease while, fortunately, most did not. A death from lupus was a reportable event.¹¹

Libman and Sacks in 1923 described an atypical form of verrucous endocarditis in a series of cases dating from 1911 to 1922. This nonbacterial endocarditis had occurred in patients dying of a systemic disease at first unidentified by these authors. Two of the patients, however, had a facial rash resembling lupus erythematosus.¹²

Klemperer pointed out in 1941 that the histopathologic detail of these vegetations and the other systemic lesions of lupus erythematosus was characterized by fibrinoid necrosis. This term referred to collagen fibers that pathologically assume tinctorial and structural qualities resembling the fibrin of clotting blood. The blood vessels—the smaller arteries and the capillaries—affected in lupus erythematosus are the primary sites of the injury. The resultant tissue damage is responsible for the vascular, endocardial, renal, and other abnormalities in the disseminated disease.¹³

Neumann in 1880 had called this abnormality "fibrinoid degeneration," to describe the deeply eosinophilic substance that forms among the connective tissues in several conditions. The alternative process of fibrinoid degeneration represents a physicochemical alteration of the interfibrillary ground substance.¹⁴

On these grounds, Klemperer grouped systemic lupus erythematosus and diffuse scleroderma as collagen or connective tissue diseases, but the concept remains hypothetical. They are multisystemic entities that over-

10. M. Kaposi. Cited by John F. Madden, "Acute disseminated lupus erythematosus," *Arch. Dermatol. Syphilol.*, 1932, 25, 854-75.

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13. Paul Klemperer, Abou D. Pollack, and George Baehr, "Pathology of disseminated lupus erythematosus," *Arch. Pathol.*, 1941, 32, 569-631.

14. E. Neumann, "Die Picrocarminfärbung und ihre Anwendung auf die Entzündungslehre," *Arch. f. mikr. Anat.*, 1880, 18, 130-50.

lap in their manifestations. For want of a better alternative, the term is still in use, sometimes modified as collagen vascular disease. The striking alterations of extracellular components of connective tissue are the common denominator.¹⁵

Fibrinoid degeneration is a purely descriptive term that represents the result of either impregnation with fibrin, disintegration of collagen fibers, abnormal formation of fibrils, or swelling or chemical alteration of ground substance. It is a characteristic finding in vasculitis and allergy to foreign proteins, as well as some other types of inflammation where hypersensitivity can be excluded.

AUTOIMMUNE DISEASE

A protein or polysaccharide introduced into an animal of a different species constitutes an antigen. The recipient animal then produces in the blood globulin proteins termed antibodies that react specifically with each antigen.

Egg white can be inoculated, for instance. Several days later blood is drawn from the animal. When the separated fresh serum is mixed with a sample of the egg albumin, the two will react and form a precipitate. However, this will not happen unless the blood is freshly drawn. The serum contains a labile series of substances that participate in antigen-antibody reactions. When the antigen is later mixed with corresponding antiserum they will precipitate as a complex only if fresh normal serum is added to the reagents. This labile element of normal serum is termed complement.

In connective tissue diseases, the inflammation of different organs is associated with the presence of immune complexes. The antigens are native not foreign, and they do not include collagen. Autoimmune reactions mediated by circulating complexes are characteristic of lupus erythematosus. Healthy tissue is attacked indirectly, through the mediation of the immune complexes. The pathology of systemic lupus is attributable to the deposition of antigen and antibody complexed with complement.

Complex mediated inflammation is intimately involved in the damage to tissue in systemic lupus. Immunofluorescent staining reveals the presence of such complexes in the joints and the renal glomeruli. A migratory

15. Paul Klemperer, Abou D. Pollack, and George Baehr, "Diffuse collagen disease," *J. Am. Med. Assoc.*, 1942, 119, 331-32; Paul Klemperer, "The concept of collagen diseases," *Am. J. Pathol.*, 1950, 26, 505-19.

symmetrical polyarthralgia of the limbs occurs in most patients. The kidneys are involved in about half of all patients by immune complexes in the glomerular tuft arterioles, and this may lead to a nephrotic syndrome and proteinuria.

Explanation of the etiology of this disease began in 1948. Hargraves at the Mayo Clinic noticed the presence of a new element in systemic lupus erythematosus. He and his coworkers observed the phenomenon of the lupus erythematosus (LE) cell in preparations of bone marrow from patients with the disease. For the first time, systemic lupus was distinguishable from discoid lupus by a laboratory test.

This LE cell occurred only in vitro and not in direct smears of fresh marrow. It was found serendipitously, and at first only, at the Mayo Clinic. The hematologist there was in the habit of drawing the bone marrow from a patient in the hospital, preserving it in anticoagulant, then walking a few blocks to the clinic carrying the sample in his shirt pocket. This provided time, incubation, and opportunity for the engulfment and partial digestion of free, lysed nuclear material. Such chromatin was then seen intracellularly within a phagocytic vacuole as a homogeneous, purple staining mass.¹⁶

When the test is repeated under similar conditions, the LE cell appears characteristically in cases of acute disseminated lupus. The phagocyte is usually a mature neutrophilic polymorphonuclear leukocyte. Rosettes of cells may develop as neutrophils cluster around the amorphous nuclear material.

The bone marrow of patients with lupus erythematosus is not actually required for the test. Typical LE cells can be reproduced when normal marrow is incubated with blood from patients with systemic lupus. Even the bone marrow is not necessary; the LE cell is found among the white blood cells of the venous blood of these patients. It is even produced in clotted blood after screening out the fibrin. Coagulation of the blood evidently provides a structure where phagocytes can wander and engulf damaged nuclei.

Soon afterwards Haserick found the serological factor inducing the LE cell. A gammaglobulin fraction circulating in the blood of systemic lupus patients mediates its induction. The LE factor is released during the

16. Malcolm M. Hargraves, Helen Richmond, and Robert Morton, "Presentation of two bone marrow elements: The 'Tart' cell and the 'L. E.' cell," *Proc. Staff Mgt. Mayo Clin.*, 1948, 23, 25-28; M. M. Hargraves, "Discovery of the LE cell and its morphology," *Mayo Clin. Proc.*, 1969, 44, 579-99.

clotting of affected blood in vitro or by incubation of heparinized blood. The consequent damage to leucocytes allows antinuclear antibodies to penetrate the cells and attach themselves to nuclear antigens.¹⁷

The LE factor acts on dead cells or exposed nuclei and becomes bound to nuclear material, which is then released as an amorphous mass. Neutrophils phagocytose this unstructured material coated by antinuclear antibody. This is an immunologic phenomenon that requires the presence of complement. Antinuclear antibodies composed of IgG immunoglobulin molecules induce LE cells, while those constituted of IgM immunoglobulin molecules do not. This probably represents an inability to fix complement rather than a difference in antigenic specificity.¹⁸

Other gammaglobulins besides the LE factor react with various nuclear constituents, but they are incapable of inducing the LE cell themselves. Precipitation, complement fixation, and other tests show them to be true antibodies that react with deoxyribonucleic acid and proteinaceous nuclear histones. These complex molecules do not actually become depolymerized. The normal histone is simply substituted by another protein more firmly binding to DNA, probably the LE factor itself.¹⁹

Gradually it was realized that the presence of the LE factor carries a significance similar to a biologic false positive serological test for syphilis. Patients without history, symptoms, or signs of syphilis had already been encountered whose Wassermann tests appeared positive.

In 1907 Wassermann, Neisser, and Bruck discovered in the blood of syphilitic patients an antibody detectable by the newly conceived complement fixation test. Extracts of fetal liver infected by *treponema pallidum*, the causative spirochete of syphilis, constituted the first substrate. The test is not dependent on a specific component of the *treponema*, however. In fact, normal fetal liver serves equally well. Alcoholic extracts of many different human and even animal tissues can be utilized in the complement fixation test and flocculation tests for syphilis. All evidently detect the same Wassermann antibody, known as reagin. The antigen used currently is a highly purified lipid extract of beef heart termed cardiolipin.

17. John R. Haserick, Lena A. Lewis, and Donald W. Bortz, "Blood factor in acute disseminated lupus erythematosus. I. Determination of gamma globulin as specific plasma fraction," *Am. J. Med. Sci.*, 1950, 219, 660-63.

18. Claude Blondin and Frederic C. McDuffie, "Role of IgG and IgM antinuclear antibodies in formation of lupus erythematosus cells and extracellular material," *Arthritis Rheum.*, 1970, 13, 786-97.

19. L. E. Glynn and E. J. Holborow, "Immunological aspects of rheumatoid disease: a review," *Ann. Rheum. Dis.*, 1960, 19, 197-208.

Reagin is undoubtedly an antibody but the corresponding antigen is not a component of the treponema. It is a lipid component of some abnormal tissue that develops during infection with treponema, but is formed in other circumstances too.

The first specific laboratory examination for syphilis was the treponema pallidum immobilization (TPI) test of 1949. After this test was developed, the combination of the sensitive Wassermann and the specific TPI tests began to indicate the extent of biologic false positivity. The presence of reagin antibody in the absence of syphilis often indicates the existence in the patient of one of the collagen diseases.

Positive nonspecific serologic tests for syphilis in patients with systemic lupus are associated with the presence of autoantibodies to the nuclei of many cells. The fluorescent antinuclear antibody or F-ANA test has now become the standard screening test for systemic lupus. However, nuclei contain several other potential autoantigens besides native double-stranded DNA. They include single-stranded DNA and other extractable nuclear material, comprising ribonucleoprotein and another nucleoprotein or histone that is not susceptible to ribonuclease. The various autoantigens produce varied patterns of fluorescence which tend to suggest different diseases.

Immunochemical techniques have identified several autoimmune antigen-antibody systems operative in systemic lupus. The complexes found in the kidney and pathogenetic for the nephritis are composed of DNA antigen and antiDNA globulin. Other immunological tests usually positive include the latex test for the human immunoglobulin factor of rheumatoid arthritis. Antibodies to red blood cells are often present and identified by the Coombs direct antiglobulin test for immunoglobulins on the erythrocyte surface membrane.

Patients with neonatal, complement deficient, or subacute cutaneous lupus erythematosus may have serologic abnormalities, sometimes with negative ANA tests. They do not constitute a clinical, serologic, or genetically homogenous group, but can exhibit subacute, recurring, superficial, nonscarring, cutaneous lesions, without serious renal disease. In these cases, another antibody may be present, named anti-Ro or SS-A for Sjogren's Syndrome. This antibody also occurs in twenty percent of patients with systemic lupus and in about seventy percent of cases of Sjogren's syndrome.²⁰

20. Richard D. Sontheimer, "Subacute cutaneous lupus erythematosus," *Med. Clin. North Am.*, 1969, 73, 1073-90.

TREATMENT OF LUPUS ERYTHEMATOSUS

Both discoid and systemic cases of lupus erythematosus used to be treated by the administration of quinine. Jadassohn's therapy in 1904 was chiefly symptomatic but included the specific administration of quinine. The treatment of patients with this disease was still essentially similar thirty and even forty years later.²¹

During the World War II a note appeared in an eastern European journal, not available in the West until after the war, that mepacrine was of benefit in this disease. Apparently unaware of this report, Page in 1951 made the first mention in English of the use of mepacrine in lupus erythematosus, publishing a series of cases successfully treated.²²

This synthetic aminoquinoline antimalarial drug, known as Atabrine in the United States, had originally been developed to replace quinine. In both World Wars the normal supply of quinine from the importation of cinchona bark suffered interruption. Atabrine became the drug of choice for administration to countless Allied soldiers in malarious zones.

The new antimalarials were then employed in the management of lupus erythematosus. Mepacrine was prescribed extensively in the early 1950s but caused objectionable staining of the skin. Chloroquine replaced mepacrine in the late 1950s, but its use was then in turn abruptly curtailed when numerous cases of retinal damage were reported.

Hydroxychloroquine can give good results in many cases of chronic cutaneous lupus erythematosus and is the only aminoquinoline now approved in the United States for this purpose. Long term administration is warranted for systemic lupus erythematosus, but relapse may follow discontinuance.

Hydroxychloroquine, however, is chronically toxic to the eye. It can produce objective retinopathy in the form of pigment stippling of the maculae, visual field constriction to a red test object, and scotomata. The fundoscopic pigmentation noted may be of a minor nature, but it is a reason for discontinuation of administration of the drug.²³

Both discoid and systemic forms of lupus erythematosus can be treated by hydroxychloroquine at a low daily dose without side effects.²⁴ In the

21. Paul A. O'Leary, "Disseminated lupus erythematosus," *Minn. Med.*, 1934, 17, 637-44.

22. Francis Page, "Treatment of lupus erythematosus with mepacrine," *Lancet*, 1951, 2, 755-58.

23. J. G. Lanham and Graham R. V. Hughes, "Antimalarial therapy in systemic lupus erythematosus," *Clin. Rheumatol. Dis.*, 1982, 8, 279-98.

24. K. Pavelka, Jr., K. Pavelka, Sr., Z. Peliskova, et al., "Hydroxychloroquine in the treatment of rheumatoid arthritis," *Rheumatol. Dis.*, 1989, 48, 542-46.

treatment of episodes of acute disease, however, the antimalarials are ineffective, and systemic corticosteroids are required.

Since 1929 it had been known that the lives of adrenalectomized animals could be prolonged by the administration of extracts of the adrenal cortex. Within a few years many individual steroids were isolated from preparations of this gland. Hench and Kendall discovered in 1949 that two of these, namely cortisone and hydroxycortisone, possessed the ability to relieve symptoms of rheumatoid arthritis. Both compounds soon proved to be highly effective in the treatment of systemic lupus erythematosus.

At first, the preparation of these compounds required a great effort of synthesis from bile acids in numerous steps. This was based on extended research in several laboratories. One of the key operations was a method discovered by Kendall, for which he was awarded the Nobel Prize in 1950.

Pharmaceutical industry chemists were eventually able to adapt this lengthy synthesis to large scale operations. The amount of ox bile available for use in the original method soon became inadequate. Many other starting materials for the synthesis of steroids were then investigated. Finally, they were overtaken by the new practical approach of microbiological oxidation. A further advance was Hershberg's discovery that the dehydro derivatives are considerably more active than the parent hormones. Commercial production of these drugs soon began and their supply became adequate in the 1950s.²⁵

Lupus erythematosus was soon found to be one of the many diseases in which the corticosteroids exerted the most gratifyingly beneficial effects. Modern treatment of discoid disease with hydroxychloroquine and topical fluorinated steroids is effective in many instances. But oral and parenteral corticosteroids have proved to be literally lifesaving for patients with systemic disease.

25. Louis F. Fieser and Mary Fieser, *Organic Chemistry*, 3rd ed. (New York: Reinhold, 1956), pp. 977-89.

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The History of Lupus Erythematosus

From Hippocrates to Osler

C. Douglas Smith, MD, FRCP(C),* and Margaret Cyr†

"Royal diseases result from royal eating habits, for instance lupus and gout, which rarely take up residence in those who lead frugal lives and work hard."¹⁴

A LATE MEDIEVAL SERMON

The history of lupus erythematosus has been the subject of a number of excellent reviews.^{34,48} In this article we will concentrate on the period beginning about 400 BC with Hippocrates' description of cutaneous ulcers. We will then cover the evolution of the term lupus, its application to skin diseases, and the early descriptions of discoid lupus. We will end at the turn of the 20th century with the emergence of the concept of lupus erythematosus as a systemic disease. We hope to clarify a number of points of controversy, particularly with respect to the contributions of Sir William Osler.

EVOLUTION OF THE TERM LUPUS

Prior to its introduction into the medical literature, the term lupus (Latin for wolf) was used commonly by the Romans. The wolf was a prominent beast of prey and was said to have traveled in large packs, hunting and carrying off livestock. Wolves were frequently depicted in Roman poetry and art and were the subject of a Roman ritual called *lupercalia*, aimed at driving them away. The term *lupus* was first applied to cutaneous diseases during the medieval period. It is not known why the term was given a medical connotation. Some have suggested it was because the skin lesions were reminiscent of a wolf gnawing, eating away and ravaging the flesh.^{3,47} Others have speculated it was applied to lesions possessing the ability to devour flesh.³⁶ Herbernus of Tours, c. 916 AD, in his *Miracles of St. Martin* used the term lupus in his description of the healing of Eraclius (whom he called Hildricus), Bishop of Liège, at the shrine of St. Martin in Tours. A thorough account of the healing of Eraclius is found in the Foundation Charter of the College of Canons of St. Martin of Liège, c. 963 AD.

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Author Unknown c. 963 AD

"He (Eraclius) was seriously afflicted and almost brought to the point of death by the disease called lupus . . . The location of the disease . . . was not to be seen, nonetheless, a sort of thin red line remained as a mark of the scar."¹⁴

Prior to this many skin diseases were classified under the term herpes (Greek meaning to creep). Several authors have suggested that lupus may have been included in what Hippocrates termed *herpes esthiomenos*.^{32,42}

Hippocrates (460–375 BC?)

"The diseases of spring are, maniacal, melancholic, and epileptic disorders, bloody flux, quinsy, coryza, hoarseness, cough, leprosy, lichen alphas, exanthemata mostly ending in ulcerations, tubercles, and arthritic diseases."²³

After the decline of the Greek empire in 100 BC the Romans dominated the western world for the next 600 years. Greek medicine and medical terminology (including herpes esthiomenos) flourished since the majority of the physicians were Greek. The fall of the Roman empire was followed by the medieval period. Skin diseases may have been common during the medieval period due to a host of factors including lack of domestic hygiene and poor diet. Several terms were applied to morbid skin diseases. Herpes and herpes esthiomenos were carried over from the classical period. Leprosy (derived from the Greek word *Lepra* meaning scaly) was a collective term encompassing many scaly eruptions probably including lupus vulgaris, cancer, and leprosy. New terms were introduced such as Rolandus' (c. 1330) *noli me tangere* for cancer of the face, which was derived from the biblical passage "touch me not."

Virchow had difficulty elucidating what lupus implied to the writers of the medieval and renaissance periods. This prompted a review of the works of Rogerius (1230) and Rolandus (1300) from the school of Salerno. According to Virchow, from Rogerius (1230) to Manardus (1530) the term lupus implied boils of the lower extremities while skin diseases of the face were classified under the heading *noli me tangere* and sometimes under the heading herpes esthiomenos. Rogerius and Paracelsus did not identify lupus with herpes esthiomenos. The association was put in the foreground by later authors.⁴⁹

Paracelsus (1493–1541)

"Different is consolidia lupi, different are Esthiomenos, different are fistula, different are cancri."⁴⁹

After the year 1500 AD physicians attempted to limit the use of the term lupus to skin afflictions of the face, but they had few imitators.³⁴ Despite the attempts of Hieronymus Mercurialis (1520–1600), Daniel Turner (1667–1740), and Joseph Jacob Von Plenke (1738–1807) at classifying skin diseases, dermatologic terms continued to be used interchangeably.

Robert Willan (1757–1812), a British physician working in London, brought order to the study of dermatology at the turn of the 19th century. In 1790 Willan presented a method of classifying skin diseases based on clinical

observation. The earlier attempts of Mercurialis, Turner, and especially Von Plenke provided a basis for Willan's work.²⁸ Color illustrations (an innovation of Willan) of skin diseases were published in his *Manual on Skin Diseases*. The difficulty and expense in producing the engravings created enormous delays in publication. Willan's system clearly differentiated *noli me tangere*, lupus, and herpes. Due to his untimely death, Willan's work was completed by his student Thomas Bateman. According to Bateman, Willan classified vesicular diseases under the heading of herpes, and destructive or ulcerative skin diseases of the face and nose under the heading of lupus.

Willan as reported by Bateman (1810)

"Of this disease (lupus) I shall not treat at any length; for I can mention no medicine, which has been of any essential service in the cure of it, and it requires the constant assistance of the surgeon, in consequence of the spreading ulcerations, in which the original tubercles terminate.

"The term was intended by Dr. Willan to comprise together with the *noli me tangere* (do not touch me) affecting the nose and lips, other slow tubercular affections, especially about the face, commonly ending in ragged ulcerations of the cheeks, forehead, eyelids, and lips, and sometimes occurring in other parts of the body where they gradually destroy the skin and muscular parts to considerable depth. Sometimes the disease appears in the cheek circularly, or in the form of a sort of ringworm, destroying the substance, and leaving a deep and deformed cicatrix."²

Several cutaneous disorders, notably lupus vulgaris, were classified under the heading lupus. The work of Willan and Bateman was remarkable in that their classification system succeeded even though it depended entirely on direct observation. Their classification system influenced the history of dermatology since it succeeded in standardizing dermatologic terminology. It remained for later authors to subclassify Willan's lupus into lupus erythematosus and lupus vulgaris.

EARLY DESCRIPTIONS OF DISCOID AND SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

After the death of Willan, the Paris school of dermatology rose to international prominence. The St. Louis Hospital was constructed in Paris in 1612 to handle plague victims and later served as an annex to the Hotel Dieu Hospital. It was in this setting that the first clear description of lupus erythematosus emerged. Conditions were deplorable and patients were placed together regardless of sex, age, or disease. In 1801 the St. Louis Hospital began to specialize in the treatment of chronic contagious skin diseases. Physicians catered exclusively to the St. Louis and were selected on the basis of a rigorous examination. From these beginnings several key characters in the history of lupus erythematosus emerged: Biett and Cazenave.

Laurent Theodore Biett (1781–1840), a student of Bateman and Alibert, co-founded the Dermatological Saint Louis Hospital. He adapted Willan's classification of skin diseases and practiced the therapeutics of Alibert. Biett did little writing and his observations were published by his pupils Cazenave (1802–1877) and Schedel in their four-edition textbook,

Abrégé Pratique Des Maladies De La Peau.^{8-11,43} According to Cazenave and Schedel, Bielt divided Willan's lupus into three types in the first (1828) edition of the *Abrégé*: (1) Lupus qui détruit en surface (lupus which destroys on the surface), (2) lupus qui détruit en profondeur (lupus which destroys at depth), and (3) lupus avec hypertrophie (lupus with hypertrophy). In the second edition of the *Abrégé* (1833) the chapter on lupus remained unchanged and the first description of lupus erythematosus was published under the name of Erythema centrifugum in the chapter on erythema.

Bielt as reported by Cazenave (1833)

"M. Bielt has described a very remarkable variety of this disease under the name of Erythema centrifugum. It is often of very rare occurrence, and appears most frequently in young people, especially in females, whose health is otherwise excellent. It attacks the face chiefly. It generally appears in the form of round red patches, slightly elevated, and about the size of a shilling; these patches generally begin by a small red spot, slightly papular, which gradually increases in circumference, and sometimes spreads over the greater part of the face. The edges of the patches are prominent, and the centre, which retains its natural colour, is depressed. There is a considerable degree of heat and redness, but no pain or itching, and each patch leaves a slight depression on the skin. The causes of this variety are unknown. It sometimes coexists with dysmenorrhoea; it is essentially a chronic affection, although its appearance would indicate the reverse."¹²

We agree with previous historical reviews that Bielt's erythema centrifugum is the first published description of lupus erythematosus.^{3,13,19,24,30,34,48} Historical reviews are discordant with respect to the date of Bielt's publication of erythema centrifugum, namely, 1828 versus 1833. 1833 is the correct date of publication and the discrepancies have been attributed to bibliographic errors.³⁰

Discoid lupus erythematosus likely existed long before 1833 but the lack of uniformity of terms makes it difficult to be certain.^{3,13,24} Early observers of lupus erythematosus have alluded to other writers: Cazenave mentions Samuel Plumbe and Hebra mentions John Erichsen of London.²⁴ Hutchinson refers to the unpublished lectures on lupus erythematosus of his professor Mr. Startin.²⁵ Early authors frequently cite Rayer's fluxus sebaceous, described in 1828 as a synonym for lupus erythematosus although this most likely represented seborrheic dermatitis.⁴⁴

In 1841 Ferdinand von Hebra (1816-1880), a Viennese physician, took charge of the "scabies station" (a clinic for contagious and noncontagious skin diseases) at the Allgemeines Krankenhaus (General Hospital of Vienna). Hebra turned the "scabies station" into one of the most eminent schools of dermatology by the mid-1800s.

In 1846, under the heading of Seborrhea Congestiva, Hebra discussed lupus erythematosus noting two types of lesions—disc-shaped patches and smaller confluent ones,²¹ and he introduced the famous butterfly simile for the malar rash.²⁰ Jarcho identified the correct reference after years of confusion.³⁰

Hebra (1846) as translated by Holubar

"At the beginning of this disease one can see [changes] mostly in the face, on the cheeks, and on the nose in a distribution similar to a butterfly . . .

and finally presents with sharply demarcated, vividly red and scaling lesions non-itching, non-oozing, and non-eroded."²⁰

Cazenave published the fourth edition of his textbook, the *Abrégé*, in 1847. Erythema centrifugum remained in the Erythema chapter but was also included in the separate chapter on Lupus as a type of *lupus qui détruit en surface* (lupus which destroys on the surface). No explanation for this modification was provided. Five years later Cazenave published a review article on lupus in the journal *Annales des Maladies de la Peau et de la Syphilis* (1851) in which he expanded his description of erythema centrifugum by noting skin lesions of atrophy, telangiectasia, fixed erythema, adherent scaling, and follicular plugging.⁶ Observing more advanced cases prompted Cazenave to rename erythema centrifugum, calling it lupus erythemateux, and to classify it as a fourth variety of Willan's lupus.

Cazenave (1851)

"So, in order to not bring closer together, on the contrary to separate the forms that seem to me to differ between themselves by their essence, I divide lupus into: 1) Lupus erythemateux, 2) Tuberculous lupus, 3) Ulcerating lupus 4) lupus with hypertrophy."⁷

Cazenave's terminology was accepted by his contemporaries, including Hebra.

Ferdinand von Hebra (1866)

"Seborrhoea congestiva: I may take this opportunity of referring to the complaint which I have elsewhere described under this name. . . . Six years later, in 1851, M. Cazenave wrote a paper on a disease which was called by him the Lupus erythematosus and which I found to be previously described by myself under the name which I have just mentioned. Since that time I have had repeated opportunities of examining cases of this disease, and have been able to keep several of them under observation during a long period. And I have been induced to adopt M. Cazenave's name for it in preference to that which I had myself originally chosen. For this complaint, in most instances, takes a chronic course, lasting generally for many years, and when it disappears cicatrices are formed. Now, these characters certainly correspond to those of lupus rather than to those of seborrhoea."²¹

After 1851 the term lupus, when used unqualified, continued to imply lupus vulgaris due to its greater prevalence than lupus erythematosus. Lupus vulgaris may have been included in Hippocrates' herpes esthiomenos^{32,42} and may have existed before Hippocrates. Despite the fact that they were classified together, Cazenave, his contemporaries, and successors clearly differentiated lupus erythematosus from lupus vulgaris.

Kaposi (1880)

"No confusion in our ideas regarding lupus need be caused by the circumstance that, since 1850, a cutaneous affection, thoroughly distinct from Lupus vulgaris, has been included under the designation of Lupus, after the example of Cazenave, with the title of Lupus Erythematosus. It is quite sufficient, when we wish to indicate the form described by Willan, to speak of it as Lupus vulgaris or simply as Lupus."³²



Figure 1. Lupus erythematosus. Painted by Dr. Anton Elfinger. Date of production no longer legible.²⁴ (From Hebra F, Elfinger A: *Atlas der hautkrankheiten*. Text von Ferdinand Hebra. Bilder von Anton Elfinger. Wien Braumuller, 1856–1876.)

Figure 2. Lupus erythematosus. Painted by Dr. Anton Elfinger. Published in Hebra's *Atlas* in 1856. Note the spelling. (From Hebra F, Elfinger A: *Atlas der hautkrankheiten*. Text von Ferdinand Hebra. Bilder von Anton Elfinger. Wien Braumuller, 1856.)

The first published illustrations of lupus erythematosus appeared in Hebra's 1856 *Atlas of Skin Diseases* in which he latinized the term lupus erythemateux to lupus erythematosus and devoted two plates (Fig. 1 and 2).²² The title of Figure 2 was misspelled lupus erythematosus.³⁰ Both figures were painted by Anton Elfinger, a Swiss physician-painter. We

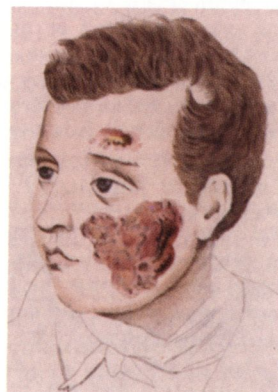
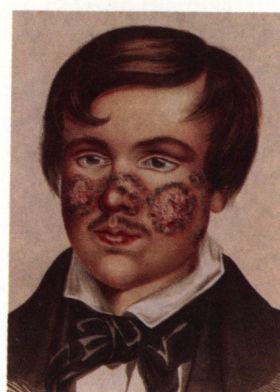


Figure 3. Lupus—Cazenave, 1838. We and others have concluded that this is not lupus erythematosus, but more likely represents lupus vulgaris. (From Cazenave PLA, Schedel HE: *Abrégé pratique des maladies de la peau*. Troisième Edition. Paris, Bachelier, 1838.)

Figure 4. Lupus marginatus, hand drawn by Edwin Meese in 1870. Published in Hutchinson's *Archives of Surgery* in 1880. Note the similarities between this and annular subacute cutaneous lupus erythematosus. (From Hutchinson J: *Archives of Surgery*. Volume I. London, J. and A. Churchill, 1889; with permission.)



agree with Holubar's historical interpretation²⁴ that Cazenave's portrait of lupus in 1838 (Fig. 3) was probably lupus vulgaris and not lupus erythematosus as suggested by others.⁴⁸

Jonathan Hutchinson was a surgeon practicing in London during the Victorian era. Although largely under-recognized he made several original observations in the study of lupus erythematosus. In his lecture on lupus erythematosus (1879) he introduced the batwing simile for the malar rash and alluded to the presence of photosensitivity.

Jonathan Hutchinson (1879)

"Under the name Lupus erythematosus, observers have denoted a malady closely allied to lupus, indeed, in many cases, absolutely identical with it, but of which the chief feature is an erythematosus patch. . . . The more common forms of erythematosus lupus are met . . . in young or middle aged adults. . . . Usually the disease begins on the nose, and a red, slightly roughened patch is produced on the middle of the organ; next, two symmetrical red patches are seen on the cheeks. . . . When the patches on the cheeks have become joined to that on the nose, a form is produced like that of a body with wings, which has been compared to a bat's wing or a butterfly . . . the patches are usually abruptly margined, more red at their edges than in the middle, rough, dry, slightly scaly. . . . Often a great number of little patches occur in a cluster, and some of them become confluent, and when this is the case the little patches, which are more or less round, are depressed in the centre and slightly raised at their edges, being what is known as disc shaped. . . . Erythematosus lupus is very rarely seen in those parts of the surface which are constantly protected by clothes.

It is also always made worse by exposure to the wind and cold. . . . Sunburn of the nose is a common exciting cause."²⁵

In 1880 Hutchinson published a description of a disease resembling what recently has been called subacute cutaneous lupus erythematosus under the heading of lupus marginatus. He believed it was a form of lupus vulgaris.

Jonathan Hutchinson (1880)

"Lupus Marginatus is a name which I have ventured to give to a very rare and very peculiar form of lupus in which the margin is extremely thin and delicate, and in which, with no visible ulceration, a very superficial scar rapidly forms in the centre. It is certainly in essential features a lupus; and it differs from lupus erythematosus in not being very vascular, and in having no tendency to symmetry."²⁶

Almost a decade later (1889) Hutchinson published the first portrait of lupus marginatus in his *Archives of Surgery* (Fig. 4).²⁷ The portrait was hand-drawn by Edwin Meese in 1870. The patient, named Hillard, was an 8-year-old boy whose outcome is unknown.

The pathogenesis of lupus erythematosus has long been a subject of controversy. It was first attributed to changes in the sebaceous glands.

Kaposi (1875)

"We are unable to adduce any very satisfactory data bearing on the cause of Lupus Erythematosus. . . . In some cases, we recognise a distinctly local cause for lupus erythematosus ie. severe local seborrhoea. . . . The condition, therefore represents a "Seborrhoea Congestiva" (Hebra), as

evinced by the chronic congestion around the orifices of the follicles, the dilation of the latter, and the hypersecretion from the glands."³³

The tuberculous theory was ignited by Koch's identification of the tubercle bacillus and the discovery of its role in the etiology of tuberculosis of the skin in 1882. The coexistence of tuberculosis in some patients with lupus erythematosus and the unfortunate naming of Leloir's lupus erythematoide (a type of tuberculosis of the skin resembling lupus erythematosus) fueled this theory.³⁵ The joint classification of lupus vulgaris and lupus erythematosus may have also contributed to the confusion. Extensive pathological studies done in the 1920s and 1930s dispelled the tuberculous theory.³⁴

THE CONCEPT OF LUPUS ERYTHEMATOSUS AS A SYSTEMIC DISEASE

Prior to 1872, lupus had been a term used to describe a chronic condition limited solely to the skin. The systemic nature of lupus erythematosus was first described in 1872 by Moriz Kaposi. Born Moriz Kohn, Kaposi was not only a student of Hebra but was also his son-in-law. Kaposi wrote the following in his textbook published in 1875 (translated into English in 1880), based on his original article in 1872:

"Since then, however, experience has shown that lupus erythematosus may not only extend more deeply locally, and may be attended by altogether more severe pathological changes than was known of at that time; but that also various grave and even dangerous constitutional symptoms may be intimately associated with the process in question, and that death may result from conditions which must be considered to arise from the local malady. Of late, therefore, Lupus erythematosus, has become a more important affection, and it has become necessary to modify, in some measure, the description usually given of the clinical character of the disease."³³

Kaposi proposed that lupus erythematosus should be classified into two types:

"From this stage of primary efflorescence, Lupus erythematosus may be further developed in a twofold manner. First, as characteristic large discs, which I shall call the discoid form. Secondly, as disseminated and aggregated small spots of the character described, which I call Lupus erythematosus disseminatus et aggregatus."³³

He then went on to describe various "concomitant symptoms":

"The symptoms which may be associated with an acute or subacute eruption of Lupus erythematosus are: 1) Nodules of the size of hazel nuts or walnuts, which are situated deeply or in the subcutaneous tissue, feel of the consistence of firm dough, are painful spontaneously and on pressure, and are covered by skin of normal colour, but pushed forward by them. . . .

2) Oedematous, tubercular, painful swelling of the consistence of firm dough, affecting the skin and the tissues around the joints of the metacarpus of the fingers and toes, and also of the larger joints, of the knees and elbows. . . .

3) Aching, boring deep-seated pains in the bones. . . . Severe pains in the large joints frequently occur in the course of the disease and are

occasionally of a nocturnal character, causing the symptoms to resemble those of syphilis. These rheumatoid pains are very often precursors of a more or less extensive outbreak of lupus. . . .

4) Adenitis—Very large, hard and painful swelling of the lymphatic glands, submaxillary and more rarely inguinal, and of the parotid, especially, occur in certain cases of Lupus erythematosus, most frequently those in which the eruption becomes rapidly developed. . . .³³

Kaposi also alluded to the occurrence of fever, weight loss, anemia, amenorrhea, dysmenorrhea, and an "increase in the catarrh of the apices of the lungs." He described erysipelas and erysipelas perstans faciei as complications and pointed out the potential for a fatal outcome:

"In the course of 2–3 weeks death ensues being preceded by increased mental disturbance, coma, sopor or by pleuropneumonia, or the fever vanishes. . . .³³

Following Kaposi's description in 1872 a number of reports of SLE emerged.^{4,5,17,18} Involvement of the mucous membranes was described by Fox in 1890.¹⁵ In 1894, Payne, a physician working at the St. Thomas Hospital in London suggested there was a "vascular disturbance causing hyperemia [and that] this circulatory disturbance is very much influenced by quinine."⁴⁰ He treated patients with large doses of quinine with some success. In 1898 at the meeting of the British Medical Association a debate was held on the nature and treatment of lupus erythematosus. In this discussion Dr. Radcliffe-Crocker commented that:

"In violently inflammatory cases he had observed good results from salicin, as well as from quinine, and less frequently, from ichfluyol internally."⁴¹

In 1902 Sequira and Balean of the London Hospital published a series of 71 cases of lupus erythematosus of which 60 had discoid and 11 had disseminated disease.⁴⁷ These authors described acroasphyxia (Raynaud's phenomenon) as a common feature. They studied the urine of 27 cases and found albuminuria to be more common in disseminated LE, which was in an active stage at the time of study. They gave a detailed account of the clinical features and autopsy findings of an 18-year-old girl presenting with a malar rash, malaise, headache, abdominal pain, peripheral edema, and hematuria (Fig. 5). She went on to develop diffuse skin involvement, dyspnea, fever, a pleural effusion (pneumococcal), and an active urinary sediment with blood, hyalin, and granular casts. At autopsy there was evidence of pneumonia involving the left lung as well as an area of wedge-shaped infarction involving the right lung, and microscopic evidence of glomerulotubular nephritis.

The contribution of Sir William Osler to the descriptions of systemic lupus erythematosus has been the subject of controversy. Between 1895 and 1904 Osler published a trilogy of papers devoted to the systemic manifestations of a variety of diseases also involving the skin.^{37–39} It is clear that most of these cases were not examples of lupus erythematosus. The first paper of the series was entitled "On the Visceral Complications of Erythema Exudativum Multiforme."³⁷

Osler (1895)

"By exudative erythema is understood a disease of unknown etiology with polymorphic skin lesions—hyperaemia, oedema, and hemorrhage—arthritis occasionally, and a variable number of visceral manifestations, of which the

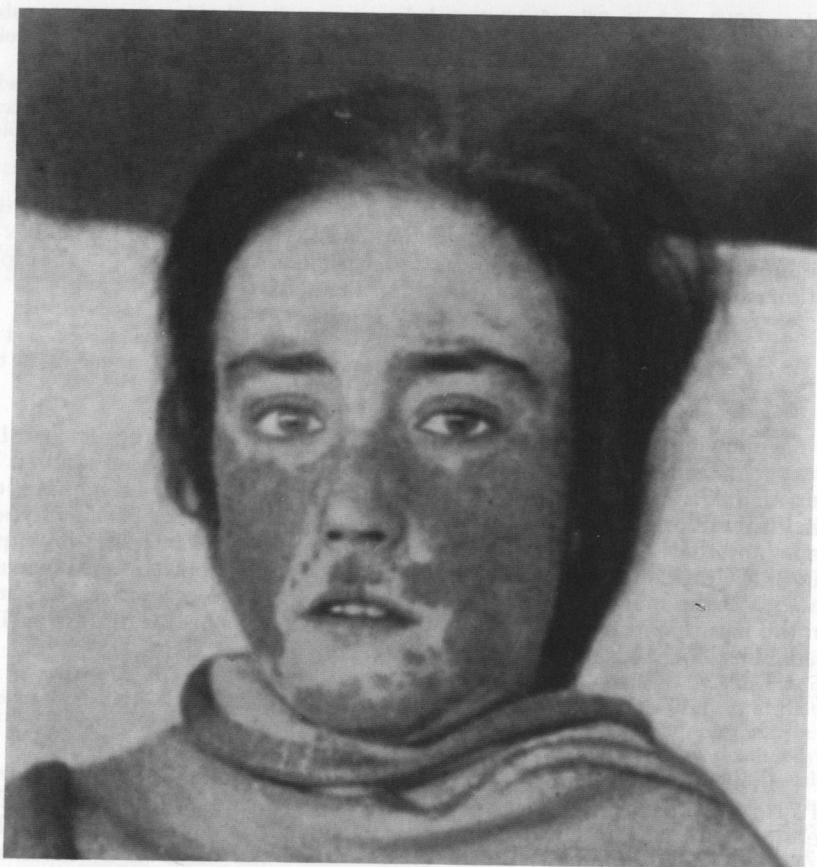


Figure 5. An early photograph of an 18-year-old woman who died and underwent a detailed postmortem examination. She was included in a review of 71 cases of SLE. (From Sequeira JH, Balean H: *Br J Dermatol* 14:367-379, 1902; with permission.)

most important are gastro-intestinal crises, endocarditis, pericarditis, acute nephritis, and hemorrhage from the mucous surfaces. Recurrence is a special feature of this disease, and attacks may come on month after month, or even throughout a long period of years. Variability in the skin lesions is the rule, and a case may present in one attack the features of an angioneurotic oedema, in a second of a multiform or nodosa erythema, and in a third those of peliosis rheumatica. The attacks may not be characterized by skin manifestations; the visceral symptoms alone may be present, and to the outward view the patient may have no indications whatever of the erythema exudativum."³⁷

Osler described 11 cases in his 1895 paper.³⁷ He titled the second and third papers: "On the Visceral Manifestations of the Erythema Group of Skin Diseases." In the 1900 paper he described seven patients.³⁹ In the third paper of 1904 Osler discussed a further 11 cases and summarized the features of his total series of 29 cases.³⁸ Although Osler did not recognize them as such, the majority of his 29 cases consisted of patients with

Henoch-Schönlein purpura, while a few likely had erythema multiforme, angioedema, and gonococcal septicemia.

Osler (1904)

A criticism has been made of my previous papers that I had jumbled together a motley group of cases, some of purpura, some of angioneurotic oedema, others of peliosis rheumatica, others, again, of exudative erythema. I did so on purpose, for I was seeking similarities, not diversities, and I refrained as much as possible from the use of specific terms, often indeed not knowing what to call a case watched for a long period."³⁸

Only two of Osler's 29 cases clearly had systemic lupus erythematosus—cases XIX and XXVI published in the third paper of 1904. Case XIX was a 15-year-old girl who presented with a photosensitive malar rash and went on to develop joint pain, pleuritis, fever, and splenomegaly. She died 7 months later with nephritis and uremia. Case XXVI was a 24-year-old woman whose initials were L. E. She presented with a malar rash and her course was complicated by the development of fever, chills, lymphadenopathy, and pneumonic consolidation. Osler also noted that "About two weeks ago the left leg became swollen and she had a thrombus in the femoral vein." She died of nephritis and a uremic convulsion 9 months after presentation. Osler clearly recognized that there were similarities between this case and case XIX. Ironically, others had suggested a diagnosis of lupus erythematosus in case XXVI but Osler made no further mention of it.

Osler (1904)

"Toward the end of the summer, when at the Thousand Islands, a rash began on the face, chiefly on the nose and cheeks. It looked the doctor said, like lupus erythematosus. It persisted and troubled her a great deal.

Dr. Fox, of New York, who only saw her once, writes that he thought it looked like an acute lupus erythematosus."³⁹

In 1904 Jadassohn published a 125-page review of lupus erythematosus with nine pages of references.²⁹ He discussed both discoid and systemic LE and included sections on the clinical features, pathologic anatomy, etiology and pathogenesis, diagnosis, prognosis, and treatment. He referred to the frequency of constitutional symptoms, and involvement of joints, serous and mucous membranes, and kidneys. In our opinion, authors such as Kaposi, Sequeira, Balean, and Jadassohn most deserve the credit for early descriptions of the systemic features of lupus erythematosus.

Since the beginning of the 20th century a number of important discoveries have been made, vastly improving our understanding of the pathogenesis of the disease as well as its diagnosis and treatment. The history of these developments is beyond the scope of this article and has been the subject of a number of excellent reviews.^{34,48}

SUMMARY

Hippocrates (460-375 BC) was the first to describe cutaneous ulcers under the heading of herpes esthiomenos. From what we can tell, Herbernus of Tours was the first to apply the term lupus to a skin disease in 916 AD. Following this, a number of terms including lupus, *noli me tangere*, and herpes esthiomenos were used to describe cutaneous ulcers. Willan (1757-

1812) expanded the classification of skin diseases using the term herpes for vesicular diseases and lupus for destructive and ulcerative diseases of the face. The first clear description of lupus erythematosus was by Bielt and was reported by his student Cazenave under the term erythema centrifugum in 1833. In 1846 Hebra, under the name of Seborrhea Congestiva described disc-shaped patches and introduced the butterfly simile for the malar rash. In 1851 Cazenave renamed erythema centrifugum, calling it lupus erythematosus and gave a classic description of discoid lupus erythematosus.

In 1872 Kaposi subdivided lupus into the discoid and systemic forms and introduced the concept of systemic disease with a potentially fatal outcome. Hutchinson alluded to the photosensitive nature of the rash and may have provided the earliest description of what is now called annular subacute cutaneous lupus. In 1894 Payne used quinine in the treatment of patients with LE and postulated the presence of a vascular disturbance. In 1902, Sequira and Balean published a large series of patients with discoid and systemic LE and provided clinical and pathologic details of a young woman who died of glomerulonephritis. In 1904, Jadassohn published an exhaustive review of discoid and systemic LE, including clinical features and pathologic findings.

Between 1895 and 1904 Sir William Osler published 29 cases of what was termed the erythema group of diseases. Perhaps his major contribution was to show that skin diseases could be accompanied by a variety of systemic manifestations. In retrospect most of his patients suffered from diseases other than SLE and it was only in his 1904 paper that two cases with SLE were described. He did not acknowledge this diagnosis in his cases and we share the viewpoint that his contribution to the study of SLE has been overemphasized.

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Epidemiology of Systemic Lupus Erythematosus

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A fundamental element of epidemiology is the study of the uneven distribution of disease in time and space and of the environmental factors associated with this unevenness. Seeking the determinants of disease, whether genetic or acquired, the studies of the epidemiologist may include examinations of large populations, discrete ethnic groups, small families, and putative environmental toxins whether infectious or noninfectious; the observational techniques range from direct clinical ones to those of complex molecular biochemistry; the statistical methods vary from the simplest numeric counts to derive incidence and prevalence to the most complex multivariate techniques in order to discern degrees of association. In this essay, I shall confine myself to reviewing studies of the prevalence of systemic lupus erythematosus (SLE) in large populations and shall suggest interpretations that might account for why there seem to be important differences among large populations in the prevalence of SLE. My excuse for hypothesizing beyond the facts is taken from Frost, as cited by Masi,³⁰ in an excellent article on the epidemiology of SLE, which I recommend to the reader: "Epidemiology at any given time is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation."¹⁶ The data that interest me are those showing a high prevalence of SLE among Chinese in China, whereas the prevalence of SLE among Chinese in San Francisco is consistent with the Chinese representation in the general community and the prevalence of SLE among Chinese in Hawaii is about intermediate between that in China and San Francisco. In contrast, black women in San Francisco and New York City show a prevalence of SLE about four times their representation in their local communities, and the disease is common in Jamaica; but in Africa itself, SLE is rarely observed. Most of the epidemiologic studies are in Chinese women and black women, but I shall also review findings in American Indians; there are suggestive findings, too, among Puerto Ricans, Polynesians, and Asian Indians.

POPULATION STUDIES

SLE in Black People

The number of patients with SLE whose diagnosis was based upon the preliminary criteria of the American Rheumatism Association (ARA)⁷ was

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Treatment of systemic lupus erythematosus: from cod-liver oil to cyclosporin

Thomas G Benedek

We now think of systemic lupus erythematosus (SLE) as a multisystemic disease that may include specific, more or less extensive, skin lesions. In the the 19th century (discoid) lupus erythematosus (DLE) was solely a skin disease and was studied largely by dermatologists whose main interest was in differentiating these lesions from lupus vulgaris (cutaneous tuberculosis). "Disseminated LE" initially meant that the skin lesions were extensive, but this term became ambiguous when it was subsequently applied to patients with both cutaneous and visceral symptoms. One reason that SLE was regarded as a rare disease was that the diagnosis required the presence of characteristic skin lesions; patients with appropriate visceral findings but normal skin received various descriptive circumlocutions. It was first suggested in 1936 that such a case might actually be SLE,¹ and in 1937 that DLE and SLE might be the same non-bacterial disease, differing only in severity.²

The therapeutic history of DLE is longer than that of SLE, but it has been just as frustrating. In London, Jonathan Hutchinson wrote in 1880:³ "We must improve the patient's state of nutrition with tonics, good food, bracing air, cod-liver oil, and the judicious use of stimulants. To all these, arsenic—the specific for psoriasis—may usually with much advantage be added. . . . We must abstain from enfeebling the health by iodides and mercury". He was more aggressive when it came to topical treatment—"The new cell-growth must be destroyed, eradicated without delay and without flinching"—which he attempted with caustics or a cautery.³

Louis Duhring, professor of dermatology at the University of Pennsylvania, contrariwise advocated in 1881 the internal use of either potassium iodide or iodine-soaked starch and believed that "mercurial ointment is of service in some cases". He cautioned that caustics should be a last resort because their use was "without notable success".⁴

J M MacLeod, a London dermatologist, in 1908 was one of the first to discuss treatment in the presence of visceral symptoms: "As the exact nature of the toxins responsible where the disease is associated with such general toxins as result from nephritis, disease of the liver, rheumatism, etc, is uncertain, the appropriate antitoxin is

not available but various drugs are employed which are known to have an antitoxic action, such as quinine and salicin. . . . Besides its action on the toxin salicin is a cardiac depressant and reduces the hyperaemia in the skin". A paste of ichthyol, a crude sulphurous extract from shale, had become a favourite topical remedy because of its supposed vasoconstrictive effect.⁵ In 1913, MacLeod conceded that "The general treatment is based largely on general medical principles, and absolute reliance cannot be placed on any kind of specific form of medication".

The intravenous injection of gold compounds—the first treatment thought to be aetiological—was based on the belief that lupus erythematosus is a manifestation of tuberculosis. In view of Koch's observation in 1890 that gold cyanide was tuberculocidal in vitro, this compound was used in 1913 to treat lupus vulgaris and, later that year without benefit, to treat a case of DLE. However, this form of therapy was pursued with various organic and inorganic compounds. In 1927, Schamberg introduced aurotherapy (with gold sodium thiosulphate) for DLE in the USA.⁶ 2 years later, bismuth, usually by intramuscular injection, was tried in France, mainly because it was less toxic than gold; and in 1938, an optimistic review by Tolman⁷ in Boston stated that "Prior to the introduction of aurotherapy there was no one specific method of attack

in the treatment of [discoid] lupus erythematosus", and that "bismuth is . . . as valuable as gold and less dangerous". Gold achieved remissions in about half the cases of DLE and bismuth in a third.⁷ Both were used into the 1950s, although gold predominated.

Making sure that the patient had no visceral symptoms became a recommendation when gold therapy for DLE was considered. Thus in 1937: "The general opinion that this method of treatment is contraindicated for acute and subacute disseminated lupus erythematosus is well founded on sad experience. . . . The capillaries seem unduly sensitive not only to gold therapy but also to a wide variety of therapeutic agents. . . . This is understandable in the case of gold preparations, since it affects the structures (capillaries) attacked by lupus erythematosus itself".² Despite little documentation, a 1953 textbook⁸ retained the warning that "gold is especially dangerous in the acute phases [of LE] and probably should never be used".

Gold therapy was eclipsed by the resurgence almost simultaneously of antimalarial compounds and the advent of corticosteroids. Quinine had been introduced in 1894



**Sir Jonathan Hutchinson
(1828–1913)**

"We must improve the patient's state of nutrition".

Wellcome Institute Library, London

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on the basis of the hypothesis that it had a cutaneous vasoconstrictive effect that would counteract the lesions of DLE.⁹ In 1938 Davidson and Birt postulated that at least some cases were caused by an abnormal reaction to ultraviolet light and "quinine might in some way change the reaction of the skin to the rays".¹⁰ If the original antimalarial drug affected DLE lesions, perhaps a synthetic substitute would be more effective. This unlikely possibility was tested in 1950. A patient whose extensive DLE lesions had stopped spreading, but had not diminished, while he took quinine was switched to quinacrine. Within 2 months the lesions had resolved. The first report of treatment efficacy, by Page in 1951¹¹ included 17 cases of DLE, with excellent or "good" results in 13, and one case of SLE; she was symptom free after 10 months of follow-up. 2 years later, a report from the Mayo Clinic¹² confirmed the favourable impression with respect to DLE, but warned against giving quinacrine to patients who had "systemic repercussions".

That same year Goldman and colleagues decided to try chloroquine, the drug that was replacing quinacrine in malaria therapy "because it is distinctly less toxic, it may be found in the skin in appreciable amounts after oral ingestion, and it does not discolor the skin".¹³ Chloroquine quickly became the principal medication for DLE, even though it was found to be therapeutically equal only to gold.¹⁴ Hydroxychloroquine was introduced in 1956, 1 year before retinopathy (potentially resulting in blindness) had been first attributed to chloroquine.¹⁵ Hydroxychloroquine gradually replaced chloroquine, mainly because of its lower retinal toxicity.

The last review of SLE before the advent of cortisone stated in 1949 "There is no satisfactory treatment of disseminate lupus erythematosus".¹⁶ Shortly after an acute anti-inflammatory effect of cortisone on rheumatoid arthritis was shown in early 1949, this drug and corticotropin were tried in a few cases of SLE. In some patients there was a rapid reversal of symptoms, which had never been seen previously.¹⁷ For several years cortisone, hydrocortisone, or corticotropin were used in widely varying symptom-related doses. In 1954, prednisone and prednisolone, which are analogues of, respectively, cortisone and hydrocortisone, were introduced. Because of their lower fluid-retaining property they gradually replaced the original hormones. By 1953 corticosteroid therapy was recognised to be less effective in counteracting the nephropathy of SLE than for other manifestations.¹⁸ Then, in 1958, Ziff and colleagues¹⁹ found that when combined with an antimalarial, a lower corticosteroid dose usually had an equivalent therapeutic effect, whereas antimalarials alone were doubtfully effective against visceral signs.

The most recent important addition to the treatment of SLE has been non-hormonal immunosuppression. This began in 1951 with the intravenous administration of nitrogen mustard and was based on recent observations of favourable responses in cases of nephrotic syndrome. Dubois concluded that nitrogen mustard also benefited nephritis caused by SLE, but did not reliably counteract its other features.²⁰ The relative effectiveness of nitrogen mustard in renal lupus was confirmed, but fell into disfavour after the introduction of cyclophosphamide in 1964. Several other immunosuppressive drugs of the alkylating and antimetabolite types were tried in the 1960s, but cyclophosphamide has continued to be used the most, especially when corticosteroids have been ineffective.²¹ The cumulative dose should be reduced to a minimum because

chronic administration carries the risks of haemorrhagic cystitis and eventual bladder carcinoma. Lately, cyclosporin, a fungal polypeptide, has shown promise in refractory cases of SLE,²² although the usefulness of this potent, novel immunosuppressant may be limited by its nephrotoxicity.²²

Hydroxychloroquine remains the primary medication for DLE, with the addition of a topical corticosteroid for recalcitrant cases. About 5% of cutaneous cases evolve into SLE. 50 years ago, half of the few patients who were diagnosed with SLE survived for 4 years; now at least 90% survive for more than 10 years.²³ Some of this extra survival is due to the recognition of more mildly affected patients. However, there is no doubt that various immunosuppressive therapies have substantially prolonged life, and newer analgesics, antibiotics, shielding against ultraviolet light, etc, have also improved well-being. However, curative treatment of the spectrum of disease from mild DLE to fulminant SLE still awaits the definitive identification of the cause(s).

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