Cortisone and the burning cross

The story of Percy Ju an

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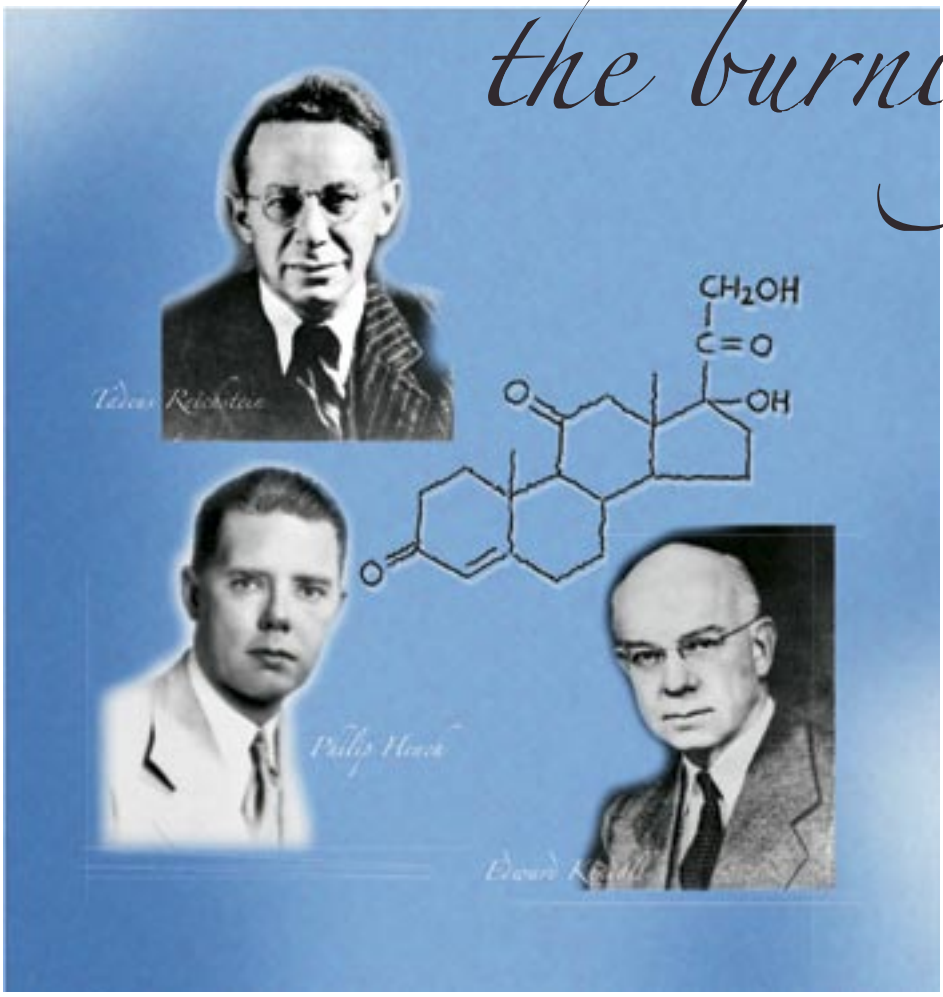

Philip Hench, Edward Kendall, and Tadeus Reichstein received the 1950 Nobel Prize for Physiology or Medicine for their discoveries relating to the isolation and use of cortisone.
Photos courtesy of the National Library of Medicine.

The author (ΑΩΑ, New York University, 1965) is research professor of medicine and director of the Biotechnology Study Center at New York University School of Medicine. In 2002 he was elected to the Accademia Nazionale dei Lincei (established in Rome in 1603) as the sole American physician member. He is a member of the editorial board of *The Pharos*, and a previous contributor to the journal.

Rheumatology, the treatment of bones and joints and widespread miseries, came late to the game of medical science. For many years my medical specialty was a descriptive art; in any meaningful way we had no idea of what was going on. The cardiologists had their cardiograms and digitalis, the endocrine people had their thyroid tests and extracts, but, despite stop-gap measures, joint doctors seemed condemned to stand idly by to watch many of their patients turn into cripples. Oh yes, we had diathermy, gold salts, paraffin injections, and, believe or not, bee venom. We knew how to treat gout with colchicine and had just learned to give penicillin to prevent rheumatic fever, but by and large our treatment of joint disease, or serious threats like systemic lupus erythematosus (SLE), was limited to aspirin, aspirin and more aspirin. All that changed in the *annus mirabilus* of our field, 1948. It's the year that cortisone was first given to a patient with arthritis. It's also a year when bigots were burning the houses of black folk in white suburbia and lighting crosses on their lawns.

At a staff meeting of the Mayo Clinic in January of 1948, Malcolm M. Hargraves described the LE cell, which permitted rheumatologists not only to make a diagnosis of SLE, but

also gave us an insight into one factor operative in the disease: we now call the process "apoptosis." Before 1950, we couldn't really tell who had SLE and who didn't; we had no clue as to why dead cells might cause auto-antibodies to appear. Hargraves's discovery of the LE cell sparked the study of autoimmunity and led us over the threshhold to science.[1]

In the same month, immunologist Harry Rose and rheumatologist Charles Ragan of Columbia described a factor in the serum of most patients with rheumatoid arthritis (RA) that clumped sheep red blood cells coated with human antibodies: the "sensitized sheep cell agglutination test." Tests for this factor not only permitted accurate diagnosis of rheumatoid arthritis, but also taught us that in RA the joints are inflamed by immune complexes directed against our own immunoglobulins. As with Hargrave's finding of the LE cell, the discovery of rheumatoid factor made it possible to make sense of yet one more of our diseases.[2]

On April 20, 1949, William L. Laurence of the *New York Times* broke news of another staff meeting at the Mayo Clinic:

> Preliminary tests during the last seven months at the Mayo Clinic with a hormone from the skin of the adrenal glands has opened up an entirely new approach to the treatment of rheumatoid arthritis, the most painful form of arthritis, that cripples millions, it was revealed here tonight.[3]

That evening, Philip Hench, Charles Slocumb, and Howard Polley reported their experience with 14 cases of rheumatoid arthritis treated with a precious material called "Kendall's compound E" or 17 hydroxy-11 dehydrocorticosterone.[4] Cortisone had entered the clinic.

Within a week, cinemas nationwide showed newsreels of cripples rising miraculously from their wheelchairs. By May of 1949, Hench and coworkers reported the "complete remission of acute signs and symptoms of rheumatoid inflammation"[5] at the Association of American Physicians in Atlantic City. In June, they added success with rheumatic fever to the cortisone legend at the Seventh International Congress of Rheumatic Diseases in New York. It was the summer I decided to follow my father into rheumatology and I will never forget the waves of applause after Hench's dramatic film clips were shown to a packed crowd at the Waldorf Astoria.

In October 1950, the Nobel committee announced that Philip Hench and the two biochemists who had painstakingly isolated and described the chemistry of adrenal steroids, Tadeus Reichstein (of the University of Basel) and Edward Kendall (of the Mayo Clinic), would receive the Nobel Prize in Physiology or Medicine "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects."[6] Hench remains the only rheumatologist among Nobel laureates. So universal was the acclaim for cortisone that the Swedish announcement of the 1950 Nobel prize in literature (William Faulkner) was almost a footnote in the world press.

There were other footnotes in the fall of 1950. On Thanksgiving Eve, November 22, a hate crime was committed in the exclusive Oak Park suburb of Chicago: "Arson Fails at Home of a Negro Scientist," headlined the newspapers. It was one of a string of cross-burnings and arson attempts in the white suburbs of Chicago. The scientist in question was Percy Lavon Julian (1899–1975), the first African-American to buy a home in Oak Park. Julian was described as "director of research in the soya products division of the Glidden Company. . . . widely acclaimed for his discovery of life-stimulating [*sic*] chemicals, [and] drugs for treatment of diseases."[7] More to the point, in November of 1950, Julian was working feverishly on the practical synthesis of cortisone via Reichstein's compound S, work that resulted in U.S. patent 2,752,339, "Preparation of Cortisone."[8]

On December 11, 1950, less than a month after Julian's house was torched in Oak Park, Hench addressed the Nobel audience at the Karolinska Institutet.[9] He rehearsed the long trail of his discovery: how in the 1920s he had first noted relief of rheumatoid arthritis in a male physician who developed jaundice; how in the 1930s he had noted that pregnancy relieved the disease in female patients; how in the 1940s he had discussed with Kendall the possibility that substance X in the blood of jaundiced or pregnant patients might be his compound E; finally, how in September of 1948 he had written to Merck for small amounts of the laboriously synthesized material to test in the clinic. His letter noted that jaundice or pregnancy brought almost immediate relief, and he promised Merck that "if any adrenal compound is of real significance in rheumatoid arthritis we would expect to see some results within a very few days."[10p174] Three days to be exact. Beginning at 100 mg/day, IM, the Mayo doctors obtained dramatic results and soon cut to a maintenance dose of 25 mg of cortisone, Hench and Kendall's new name for compound E. That's equivalent to 25 mg tapering to 5 mg of prednisone, and nowadays those results are duplicated the world over.

In his Nobel speech, Hench reminded his audience how difficult it was to manufacture practical amounts of cortisone. Merck had gotten into the steroid business during World War II, when the National Research Council subsidized a crash program for synthesis of adrenal steroids. Washington had learned that Luftwaffe doctors were experimenting with injections of adrenal extracts to keep their aviators stress-resistant at 40,000 feet, and several of Kendall's compounds (E and F especially) seemed likely candidates. Merck's Lewis Sarret came up with a complex, difficult synthesis of E from bile: by 1944 it had produced 15 milligrams from the bile of 2,500 cows![11] Hench averred, "Although none of the thirty-six steps required to convert desoxycholic acid into cortisone has been by-passed, some of the steps have been made less costly, less time-consuming, and productive of greater yields."[9p20]

His fellow laureate, Tadeus Reichstein, told his Stockholm audience that "for practical purposes [the Sarrett] method is much too laborious. In the last two years, again particularly in the U.S.A., at the cost of a considerable amount of time, much better methods have been discovered [e.g., Julian and his collaborators] . . . For after the clinical results of Hench, Kendall and their colleagues it can hardly be doubted that the future demand for these substances will be very great."[12p10]

"Future demand" was met as the cost of production of cortisone fell from $1000/gm in 1948 to $150 in 1950 to less than $7 in 2000.[10] We owe this boon to the synthesis of cortisone from vegetal sources by Percy Lavon Julian, that brilliant "Negro scientist" whose house in Oak Park was torched on Thanksgiving Eve of 1950.

Percy Julian, Ph.D. Photo courtesy of the National Library of Medicine

Percy Julian: brilliant, determined—and black

Percy Lavon Julian, of Montgomery, Alabama, was the grandson of a former slave, and son of a postal employee.[13] He worked his way through DePauw University waiting on tables, to graduate as class valedictorian with a Phi Beta Kappa key. Between teaching stints at several black colleges he received a fellowship to Harvard, where he earned an M.A. in chemistry. Since Harvard in the 1920s had no place for a black scientist, Julian applied, successfully, for a Rockefeller Foundation fellowship at the University of Vienna to work with the eminent chemist, Ernst Späth. He received his Ph.D. in 1931, having dazzled the Viennese with his skills at tennis and piano, fallen in love with opera, and acquired a long-term collaborator, Josef Pikl.

Julian and Pikl returned to DePauw, taught chemistry, and within four years came up with the total synthesis of physostigmine from the calamar bean (*Physostigma venenosum*). Physostigmine was for many years the only weapon doctors had to fight glaucoma. The bean also contained stigmasterol, an intermediate in sex steroid synthesis, and Julian sought a more abundant source of plant sterols. He wrote to the Glidden Company (a natural product giant) requesting gallons of soybean oil. This contact led to a job interview at Glidden's labs in Appleton, Wisconsin. But Appleton had a hoary statute on its books dictating that "No Negro should be bedded or boarded in Appleton overnight." Chance favored the prepared chemist and Julian was offered a far better job in Chicago as Director of Research of the Soya Products Division of Glidden. The rest is chemical history. In more than 18 years at Glidden, Julian developed "Lecithin Granules," Glidden's soya oil, Durkee's edible emulsifiers and—not incidentally—commercial syntheses of testosterone and progesterone from soybean oil. He used soy proteins to coat and size paper, to invent cold water paints, and to size textiles. During World War II, Julian invented AeroFoam®, a soy protein product that quenches gasoline and oil fires; the foam saved lives from Europe to the Pacific. Julian was granted more than 100 chemical patents and "big Pharma" still prepares hydrocortisone from compound S à la Julian, 1950.[8] In 1953, he founded his own company, Julian Laboratories, Inc., with labs in the United States and Mexico. In 1961, the company was sold to Smith Kline French for $2.3 million, "a staggering amount for a Black man at that time."[14]

In his lifetime, Julian was honored by membership in the National Academy of Sciences, a U.S. Postal Service stamp, a dozen honorary degrees, directorships galore, and three public

schools that bear his name. We also remember that this agile chemist made it possible to make cortisone from beans instead of bile so we could give it to our patients for a pittance.

References

1. Hargraves MM, Richmond H, Morton R. Presentation of two bone marrow elements: The "tart" cell and the "L.E." cell. Proc Staff Meetings Mayo Clin 1948; 23: 25–28.

2. Rose HM, Ragan C, Pearce E, et al. Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. Proc Soc Exper Biol Med 1948; 68: 1–6.

3. Laurence WL. Aid in rheumatoid arthritis is promised by new hormone. New York Times 1049 Apr 21: 1.

4. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meetings Mayo Clin 1949; 24: 181–97.

5. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex, cortisone (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis and acute rheumatic fever. Trans Assoc Am Physicians 1949; 62: 64–80.

6. The Nobel Prize in Physiology or Medicine 1950. www.nobel.se/medicine/laureates/1950.

7. Arson fails at home of Negro scientist. New York Times 1950 Nov 23: 29.

8. Julian PL, Cole JW, Meyer EW, Karpel WJ III, assignors to The Glidden Company, Cleveland, Ohio. Preparation of Cortisone. United States Patent 2,752,339. June 26, 1956.

9. Hench PS. The reversibility of certain rheumatic and non-rheumatic conditions by the use of cortisone or of the pituitary adrenocorticotropic hormone. Nobel Lecture, December 11, 1950. www.nobel.se/medicine/laureates/1950/hench-lecture.pdf.

10. Hench PK. Reflections: A Nobel prize story. Patient Care 1999; 33: 173–74.

11. Sarett LH. The partial synthesis of dehydrocorticosterone acetate. J Am Chem Soc 1946; 68: 2478–83.

12. Reichstein T. Chemistry of the adrenal cortex hormones. Nobel Lecture, December 11, 1950. www.nobel.se/medicine/laureates/1950/reichstein-lecture.pdf.

13. Witkop B. Percy Lavon Julian, April 11, 1899–April 19, 1975. www.nap.edu/html/biomems/pjulian.html.

14. Percy Julian. www.blackinventor.com/pages/percyjulian.html.

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Lament for a son

I thought I had discarded grief—
My father's grateful querying eye
Had compassed me alone, its brief
Trajectory without the cry

Of yearning for the cease of pain.
No, on the deathbed in my home
His opiated dreams' refrain
Unhooked me: I became a son.

My own child stood outside his room
Divining how one man should meet
Another in the arms of doom
No matter if the embrace were sweet.

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