

H human Health and Medicine

There were perhaps no more important discoveries in the regional laboratories than those in Peoria that led during World War II to the mass production of penicillin. (See "Penicillin and the War Years," p. 5.) The work not only helped launch the vast antibiotic industry, but the deep vat fermentation techniques used also formed the basis for future fermentation processes in many other areas. But the regional centers have made other significant contributions to human health and medicine, some as a consequence of research on crops and other plants of economic interest. Other projects have been undertaken to utilize the vast ARS collection of microorganisms located at the NRRC. Discoveries have been made by researchers in all four laboratories about steroids and hormones, new drugs from plants, and allergic and toxic reactions to food and fiber. Much of this research was later carried forward by medical research agencies, universities, and pharmaceutical companies.

After discovery of streptomycin in 1943 at Rutgers University by Selman Waksman, there was accelerated research to discover other antibiotics from among a group of soil microorganisms known as *actinomycetes*. Pharmaceutical company laboratories found chloromycetin, aureomycin, and terramycin. Researchers at several locations, including the ARS center in Peoria, discovered polymyxin, an antibiotic, in 1947, and NRRC scientists found a way to increase production of the antibiotic, as they had earlier with penicillin. In 1948, Waksman discovered neomycin, and in 1950, an NRRC team found a new form of streptomycin, produced by a different actinomycete.

An important commercial success stemmed from research at the Eastern center on rutin, a drug found by the University of Pennsylvania Medical School to help prevent hemorrhaging in small blood vessels as a result of high blood pressure. Rutin was extracted from flue-cured tobacco for the university trials, but tobacco was too expensive a source. An ERRC research team found a much better supply in green buckwheat and over several

years developed a way to extract and purify the drug from buckwheat for therapeutic use. The process was adopted by several companies and was used until a shift occurred in the 1960's from buckwheat to imported eucalyptus leaf as a source of rutin.

In 1948, the steroid cortisone was found to relieve rheumatoid arthritis, and there was an urgent demand for precursors from which to produce cortisone and other steroids. A worldwide search was conducted for plants containing these precursors, and plants were screened by the ERRC and other USDA groups in cooperation with the National Institutes of Health.

A key compound in the synthesis of cortisone is progesterone, another steroid hormone, which in turn can be made from compounds called saponin, found in certain plants. One of these compounds, diosgenin, was of particular interest. Some 6,600 plant species were collected and screened for diosgenin in the 1950's, using assay techniques developed by Eastern lab scientists. Highest yields of the compound were found in the Mexican yam, in the plant genus *Dioscorea*. Within a few years, some 70 percent of the steroids produced in the United States were made from the diosgenin in these tubers, which grow wild in Mexico, Guatemala, and South Africa.

In carrying out the search, ERRC scientists learned a great deal about steroids and about processes for converting plant saponins to cortisone. The contributions of Wyndmoor scientists were documented in scores of publications and patents, and four new saponins were discovered, characterized, and named. In addition, the work identified many new plant sources of steroids that could be converted to cortisone.

In the late 1950's, scientists at the Western lab developed tests to identify the materials in castorbean meal that caused allergic reactions in many people. Researchers not only found the allergens, but in the process they exonerated one chemical that had been blamed unfairly for the allergies. They then developed a way to inactivate one of the most potent allergens in castorbean meal.



In Peoria, chemist Richard Powell examines new accessions of plant seeds from all over the world in a systematic search for new sources of human medicines.

More than a decade later, WRRC researchers carried out basic research to identify the toxic substances in gliadin proteins in wheat. These substances are toxic only to about 1 in every 2,000 people in the United States (and as many as 1 in 300 in Ireland). The condition, known as celiac disease, is thought to be hereditary. Eventual aim of the WRRC research is to use genetic manipulation to remove the toxic gliadins from wheat.

Ellen J. L. Lew, a Western lab chemist, was part of a team that identified the toxic substances in gliadin proteins in wheat that cause allergic reactions in many people.



During the 1960's, a worldwide plant search began to find new drugs, including cancer-fighters. By the early 1970's, plant explorers, many of them USDA scientists, had collected 20,000 species, and 1,500 of them showed enough promise as drug sources to justify further study. Much of the initial analysis was carried out by NRRC researchers, in cooperation with several universities.

One of the most promising drugs discovered at NRRC was harringtonine, a leukemia inhibitor found in minute amounts in a Japanese plummyew tree, a rare Asian evergreen. Nearly a decade later, Peoria chemists succeeded in synthesizing the drug from another and more plentiful plummyew compound. Studies of the drug continue.

An inhibitor of one type of leukemia was isolated in the 1980's from *Sesbania*, a species of toxic legume that grows on the coastal plains of the South. Popularly known as coffeeweed, the plant's seeds yield a compound named sesbanimide that has demonstrated encouraging antitumor activity in tests with mice. The NRRC research, which was carried out with scientists at

Reducing Cotton Endotoxins

The Southern center has patented a way to reduce levels of natural toxins produced by bacteria on cotton plants. Called endotoxins, the poisons are believed to be a cause of byssinosis, a lung disease found in some cotton textile workers. Workers can inhale the toxin from dust created when cotton travels through various processing steps.

SRRC scientists found that washing cotton in a solution of alcohol and sodium hydroxide, or household lye, after ginning can eliminate as much as 95 percent of endotoxin before it reaches the textile mill. Cotton dust so treated has been tested on animals, which showed no ill effects. Researchers also found that heat can destroy the toxin.

Cornell and Purdue universities, has now moved forward to clinical trials at the National Cancer Institute.

Other promising anticancer drugs found through plant searches include a rare compound discovered in *Trewia nudiflora*, a tree native to tropical areas of India, and taxol, a potent drug discovered by the National Cancer Institute. Unfortunately, the only known source of taxol is the bark of the Pacific yew tree, *Taxus brevifolia*. An extremely slow grower, the Pacific yew is found only in old-growth forests of the Pacific Northwest. Not only is it a rare species, but it takes 10,000 pounds of the bark to produce one pound of taxol for clinical trials. Many conservationists fear that demand for the drug could lead to the tree's extinction.

Responding to the need for increased supplies of taxol, researchers at the Southern laboratory have established plant-tissue cultures of *T. brevifolia*, and these cultures have already produced detectable quantities of taxol. The next steps are to identify high-yielding cell lines and to work out a bioprocess for production of the drug. In late 1990, ARS scientists at another location were working on both projects.

Regional drug research has not been limited to chemicals to fight cancer. The Southern lab, for instance, while searching for new food preservatives, found three compounds that show promise in fighting *Staphylococcus* infections resistant to most antibiotics. And the Western lab has succeeded in establishing vigorous cell colonies of a plant called heavenly bamboo that produces berberine, an antimalarial drug. These and similar discoveries underscore the need to preserve the diversity of plant species throughout the world.

At the Eastern center, scientists have worked on ways to curtail production of drugs that are manufactured and sold illegally. They found, for example, that administering a chemical called ethephon to opium poppies releases the plant hormone ethylene, causing opium capsules to fall from the plant prematurely. A problem with this and similar discoveries is that many drugs sold illegally are also produced for legitimate medical purposes.