Rutin, a New Drug From Buckwheat

James F. Couch

The story of rutin begins in 1842, when it was first prepared by a pharmacist-chemist of Nuremberg, Germany, named August Weiss, who obtained it from garden rue, *Ruta graveolens*. As time went on, chemists found rutin in a number of plants.

Rutin is a yellow, crystalline powder with the formula $C_{27}H_{30}O_{16}\cdot 3H_2O$. It is only slightly soluble in water, more soluble in alcohol, acetone, and alkaline solutions, and insoluble in chloroform, ether, and the hydrocarbons. Rutin is a glycoside, which is hydrolyzed to form one molecule each of quercetin, glucose, and rhamnose when it is boiled with 2 percent sulfuric acid. Quercetin is a well-known chemical substance belonging to the class of flavonols, a class whose representatives are widely distributed in the plant kingdom. Rutin is reasonably stable in boiling water and may be recrystallized from that medium for purification. It has been the subject of many chemical studies and its chemical nature is thoroughly understood. Extensive studies by pharmacologists at the Western Regional Research Laboratory and by others have shown that rutin is nontoxic.

For a century after its discovery, rutin remained without any known use, although plants containing it were sometimes used as dyestuffs. This use disappeared with the advent of the synthetic coal-tar colors.

In 1942 chemists at the Eastern Regional Research Laboratory were studying the constituents of tobacco in a search for compounds that might be useful in some way other than smoking. In the course of the investigations, rutin was isolated from flue-cured tobacco; a Japanese chemist had found rutin in tobacco 10 years previously and the discovery had been confirmed by two German chemists in 1936. The finding of rutin in tobacco raised the question: What use can be made of the glycoside? Its only known utility, that of a dyestuff, did not appear promising, and no other use was apparent.

As a result of a complicated train of reasoning, coupled with previous experience, it occurred to me that rutin might possess a "vitamin P" action—in fact, it might be the long-sought vitamin itself. "Vitamin P" had been postulated in 1936 by a Hungarian biochemist, Albert Szent-Györgyi, to account for certain medical effects produced by citrus extracts that could not be explained by reference to ascorbic acid or vitamin C. Szent-Györgyi and his coworkers attempted unsuccessfully to isolate from citrus fruits and red peppers the substance that had this antihemorrhagic action. They did, however, obtain a mass of chemical information on it; the data pointed to the flavonols.

To test whether rutin had the same action, it was necessary to cooperate with some scientist who was already working in the field and who could conduct the tests properly. Dr. John Q. Griffith, Jr., and Dr. M. A. Lindauer, then of the Medical School of the University of Pennsylvania, had been studying the problem for several years and were using a citrus preparation known as crude hesperidin, which contained the unidentified "vitamin P." Arrangements were made for them to test the activity of rutin. Within a year Dr. Griffith was satisfied that rutin did, indeed, possess the antihemorrhagic activity characteristic of "vitamin P" preparations. The result was announced in 1943 before the Medical Society of the State of Pennsylvania and published in May 1944 in the Proceedings of the Society for Experimental Biology and Medicine. Drs. Griffith and Lindauer continued their study of rutin with special reference to its use for increased capillary fragility in hypertensive patients. A great deal of interest was aroused by the work, and other physicians began experimenting with rutin in their practices. They found that rutin is effective in a variety of hemorrhagic conditions.

As THE DEMAND for the glycoside in medical circles grew, it became apparent that tobacco was too expensive a source of rutin to permit its extensive use. A search began for a cheaper source. A thorough survey was made of plants reported to contain rutin and others likely to contain it. Eventually the green buckwheat plant was discovered to be nearly ideal as a source. It contained several times as much rutin as did tobacco, and it was cheap; the material cost of rutin could be cut to about 1 percent by changing from tobacco to buckwheat. Buckwheat is now the chief American source of rutin for commercial purposes, although much is now being made from a Chinese drug, Wai Fa, the flower buds of the Chinese scholartree.

Rutin may be obtained from dried or green buckwheat in several ways. If dried plant is to be used, the fresh buckwheat must be dehydrated under special conditions; otherwise there may be a large loss of the glycoside. Processes for conducting this drying were studied in the laboratory and pilot plant and also in actual commercial operations. There was finally developed a process for dehydrating fresh buckwheat and producing a leaf meal rich in rutin and stable under ordinary storage conditions.

The extraction of rutin from the leaf meal or the fresh plant was exhaustively studied in the Eastern Laboratory, and the findings were made available to industry. After many trials, a process was developed in which hot dilute isopropyl alcohol, a cheap and efficient solvent for rutin, is employed. By distilling the alcohol from the extract and straining off the fats, which settle out, a watery solution is obtained from which crude rutin crystallizes on standing and cooling.

Refining the crude rutin to a compound pure enough for medicinal use presented many difficulties. We had to remove impurities, some of which stuck tenaciously to the glycoside; recrystallizations caused appreciable losses of material and had to be reduced in number; contact with iron or copper vessels discolored the rutin; and the operations had to be conducted in stainless-steel tanks, stills, and filter presses, although for some operations we could use wooden tanks. Industry has adopted the successful solutions of the many problems involved in the preparation of pure rutin from the crude product.

Some 15 chemical firms now prepare rutin of medicinal grade. Their estimated annual output is 15,000 to 20,000 pounds. Many pharmaceutical laboratories are marketing dosage forms of rutin, principally tablets, for sale in drug stores.

THE FIRST APPLICATION of rutin medicinally was in the treatment of increased capillary fragility, a condition in which the smallest blood vessels become abnormally fragile and rupture, so that small hemorrhages occur. The correction of the capillary fault is known as the "vitamin P" action. The cause of the fragility is not definitely known. Some think that the vessel walls become weakened and no longer can withstand pressure exerted upon them by the blood. Sometimes the capillary walls do not rupture but become abnormally permeable, so that they allow substances to pass from the blood into the tissue spaces in larger quantities or of different kinds than normally filter through the capillary wall. The condition is referred to as increased capillary permeability. Where either of these faults is present, danger increases of retinal hemorrhage or apoplexy, particularly in people with high blood pressure.

Medical studies have shown that rutin, taken by mouth, will correct these capillary faults in a large proportion of cases. Accompanying this return of the capillary condition to normal is a decrease in the tendencies to apoplexy and retinal hemorrhage, so that patients show only the same tendency to these accidents as is shown by patients who have not had a capillary fault.

Diabetics frequently have complications of this sort, with more or less loss of vision and often blindness. Eye doctors who have studied the use of rutin in such conditions feel that, while there has not been a positive cure, the use of rutin has resulted in arresting the progress of the loss of sight and sometimes an improvement in vision, especially in young patients.

Other applications to eye diseases have been studied. Physicians report that the use of rutin in conjunction with certain miotics is of value in glaucoma. Some ophthalmologists have found it effective when combined with dicumarol in treating retinitis associated with clotting in the central vein of the retina.

Similar results have been obtained in certain types of purpura, a disease characterized by bleeding under the skin. Success in these directions led to the use of rutin to protect animals from injury by X-ray irradiation. In such cases one of the early effects of the injury is a breakdown of the capillary wall. Investigation of the subject showed that rutin does have a protective action against this type of injury.

A laboratory method for studying the possible "vitamin P" activity of various substances based on this protective action has recently been developed. The fact of protection against irradiation led to the thought that rutin may be of some use as a defense against injury by radiations from atomic bombs, particularly in borderline cases.

Rutin has been of great benefit in a disease known as hereditary hemorrhagic telangiectasia, in which numerous small hemorrhages occur, with bleeding from the gums and nose, into the stomach and intestines, and engorgement of small skin blood vessels. The loss of blood leads to anemia; sometimes the number of the red blood corpuscles goes down to 2 million. Up to the present, no satisfactory treatment has been found for this disease, which usually persists throughout life. Several cases in which rutin has been used with benefit have been reported. The hemorrhages have been controlled and the patient's health restored sufficiently to permit his return to work.

An interesting application of rutin in strengthening the capillaries was reported by Drs. Frederick Fuhrman and Jefferson M. Crismon, of Stanford University. They were studying the effects of frostbite on animals, with the aim of developing a method for protecting persons exposed to low temperatures from injury due to cold. Because in such cases one of the early effects of freezing is damage to the capillaries, the use of rutin as a prophylactic was suggested. Experiments showed that rutin is of value in protecting against cold injury. The progress of the gangrene was stopped, although usually gangrene progresses until the victim loses the entire foot or other part that has been frostbitten. When rutin was used as a protective, little tissue was lost and rapid recovery was the rule.

Rutin has also proved of value in ameliorating the severity of the symptoms in cases of hemophilia, the hereditary disease in which, through failure of the blood to clot normally, the patient bleeds excessively after injury. Often severe pain is associated with extensive hemorrhages under the skin or into the muscles. After taking rutin, there seems to be less tendency to bleed, and the pain is lessened. The patients are able to return to school and continue their studies, which were often seriously interrupted before the rutin was administered.

We have in rutin a pure substance which by its action on the capillaries is valuable in treating diseases characterized by tendencies toward hemorrhage. Such diseases include rupturing of the skin capillaries with formation of black-and-blue areas, bleeding into the retina of the eye, hemorrhage into the brain, bleeding from the kidney, and similar conditions. Many physicians regard the development of rutin as a notable advance in medical science.

JAMES F. COUCH, *a native of Massachusetts and a graduate of Harvard University, received a doctor's degree from American University in 1926. In the Bureau of Animal Industry, 1917 to 1940, he did research on the chemistry of poisonous plants, locoweeds, larkspur, lupines, milksickness, and cyanide poisoning. Since 1940 he has been a chemist in charge of the tobacco section at the Eastern Regional Research Laboratory. In 1947 the Secretary of Agriculture awarded him a gold medal for distinguished service in recognition of his studies, which led to the discovery of the medical applications of rutin. The Philadelphia College of Pharmacy and Science in June 1948 conferred upon him the honorary degree of doctor of science.*

EVERYTHING about the orange can be used to good purpose. When it is served fresh, the peel and the rag usually are wasted, but not so when it is fully processed. The peel is used in marmalade, for candied peel, for feed for cattle, and as a source of "vitamin P." Sections are canned. The juice is a base for beverages, frozen and powdered concentrates, wine, and a distilled oil used in perfume and soap. The pulp left after the whole juice has been extracted is used as a feed for cattle.

If fully processed, however, here are some of the things that can be made from it, as well as from other citrus fruits: Methane gas, which is used for fuel in one citrus pilot plant, citric acid, used for a wide variety of purposes; ascorbic acid, or vitamin C; a cold-press oil and a terpeneless oil, both used for flavoring; molasses for feed or for production of a bland sirup, yeast, and pectin; press cake for feed; dry pulp for feed or for production of "vitamin P" and pectin; naringin, a rather bitter glycoside used by the British in marmalade and beverages and also in medicine. Six classes of pectin come from citrus pulp: Slow and rapid set, used by jelly makers; medical, sometimes used as a substitute for human plasma in transfusions; confectioner, used in candies, especially gum drops, that will retain shape and consistency; pectin-albedo, used in treatment of colitis; and low methoxyl, also used in medicine. The seeds are the source of a cake for livestock feed, an oil for making salad dressing, and hulls for use in feed or fertilizer.

As Fred Lawrence, citriculturist of the Florida Agricultural Extension Service, points out, "It would be fine if demand for all these products were strong enough to make extensive production of them profitable to the grower and processor."—*Clyde Beale, Agricultural Extension Service, University of Florida.*