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THE OFFSPRING OF THE "B" FAMILY—RIBO- FLAVINE, NICOTINIC ACID, ETC.

SOON after the wonderful effect of extracts of rice polishings on polyneuritis in pigeons and beri-beri in man was discovered, it was found that a water-soluble substance present in milk, yeast, and other foods was essential for growth in rats. At that time this was believed to be identical with the substance which would cure beri-beri. Rats deprived of foods containing it would in a few weeks lose weight, become weak and anemic, and die. One grain of compressed yeast would produce signs of returning health in a few hours, and there would be an immediate resumption of growth.

Experiments beginning about 1919 indicated that the substance which protected pigeons from polyneuritis and man from beri-beri was *not* identical with the substance that made it possible for rats to grow. Yeast could be heated to a point where its nerve-protecting powers were destroyed, and still be capable of promoting growth. Moreover, some substances, such as rice polishings and wheat germ, were found to be much more potent in protecting nerves than in promoting growth, whereas the opposite was true of such things as lean meat, egg white, and milk. The upshot of it was that after about seven years of argument and experiment the growth-promoting substance was recognized as a separate and distinct vitamin, and was christened B₂ in Europe and G in America, while the nerve-protecting sub-

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stance was thenceforth known as B₁.¹

About this time Dr. Goldberger and his associates of the United States Public Health Service discovered that vitamin G, or something associated with it in yeast, eggs, meat, etc., would cure pellagra. Pellagra is a first-rank scourge of the poorly nourished Southern share-croppers who dine the year around on little besides corn meal, salt pork, molasses, and coffee. A similar disease, called black-tongue, occurs in dogs, and it, too, was found to be cured by G-containing foods. Further complications developed when it was found that substances associated with vitamin G, but apparently not identical with the pellagra-preventing substance, protected rats and chicks from skin diseases. To make a long story short, it eventually developed that vitamin G as originally conceived was in reality a whole packet of vitamins, as full of separate entities as a roach's egg case; between 1928 and 1939 new vitamins and "factors" have been popping off from the vitamin G complex like fleas from a dead dog. The principal growth-promoting factor for rats, still sometimes called B₂ or G, turned out to be a yellow dye of a group called flavines; it has now been christened by the chemical name "riboflavine." The constituent which protects man from pellagra and dogs from black-tongue turned out to be an old familiar chemical, nicotinic acid, which Funk had found associated with vitamin B₁ in rice polishings twenty-seven years ago. The skin-protector for rats, called B₆ (part of what has been called vitamin H), has recently been obtained in pure crystalline form, and its chemical identity determined. It is probably also needed by human beings; injection of it into persons suffering from deficiency of the vitamin G complex, and manifesting great weakness,

¹"F" and "G" were proposed for B₁ and B₂ in America, but "F" had already been tentatively assigned to a fatty acid found to be necessary for the nutrition of rats. Its use for B₁ would only have caused confusion.

brings almost immediate improvement. It has also been suggested that lack of it may predispose to chilblains. The skin-protector for chicks has turned out to be pantothenic acid and is probably universally needed by all living organisms. Various other factors supposed to be necessary for normal growth in birds or rats, or to prevent anemia, cataracts, gizzard lesions, failure of lactation, and even gray hair, have been described, but the distinctness of many of these is doubtful, and evidence of their need by human beings has yet to be obtained. For the present, at least, we need not concern ourselves about them as necessary parts of our daily diet.

RIBOFLAVINE

As noted above, when the principal growth-promoting member of the vitamin G family was finally unmasked, it proved to be a yellow dye of the flavine group which had long been known as a component of milk, egg white, meat, and many plant substances. Various names had been given to it according to its source, e.g., lactoflavine, ovoflavine, etc., but since these are apparently all alike, the name riboflavine, which has only chemical significance, has been approved for it. It is not easily destroyed either by heat or alkali. It forms combinations with phosphoric acid and proteins, and in the combined form acts as an enzyme which has an important function in the body in connection with oxidations. An interesting interrelation of vitamins appears from the fact that this "yellow enzyme" requires the assistance of a compound in which nicotinic acid, another of the vitamin B family, is an ingredient.

Young rats are unable to grow if deprived of riboflavine, and older animals rapidly lose weight and become unhealthy. Recently the failure of bone marrow cells to form

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mature blood corpuscles in rats, associated with *one* of the vitamin G factors, appears to have been pinned to riboflavine, and there is a possibility of riboflavine scarcity being concerned with such conditions as "aplastic anemia" in man. A very remarkable fact about riboflavine in rats has been brought to light by the observations of Professor Szent-Györgyi that over a period of five years lousiness appeared exclusively in rats on riboflavine-deficient diets. When these lousy rats were fed riboflavine they promptly lost their lice, and diseased patches of skin developed new fur. This leads one to speculate as to whether Russian and Polish peasants lack sufficient riboflavine, and whether if it were rationed out to soldiers in war time it would help to control such louse-borne diseases as typhus and relapsing fever. Within the present year speculation as to this possibility has received support from an unsuspected angle. Experimenters at Harvard have found that lack of riboflavine renders rats highly susceptible to typhus.

We still have little accurate knowledge of the extent to which animals other than rats are dependent upon riboflavine in their food, but it is not likely that any higher animals can manufacture it. It is present in the flesh, liver, kidneys, and heart, and to a less extent in other organs of various animals, but whether some animals may be able to make their own or have it made by micro-organisms in their alimentary canals without importing it with the food is uncertain. Chicks are known to need it in the food, and recently it has been discovered that dogs provided with all known or suspected vitamins except riboflavine become yellow-livered and die. A dog in a state of utter collapse, apparently staring death in the face, can be returned to health within a few hours by injection of a few milligrams of riboflavine. It is likely, therefore, that the need for

riboflavine is quite general.

The principal visible symptom of lack of riboflavine in human beings is the development of lesions of the lips and mouth. Very characteristic are red, macerated transverse streaks at the corners of the mouth. This condition has been experimentally produced by diets lacking in riboflavine, and rapidly cured by its administration. Mouths showing these lesions are common in many parts of the tropics, especially in India, and are frequently seen in rural areas of our southern states where pellagra is also common, and where grits, biscuits, and a little home-cured pork are the principal items on the menu, to the exclusion of milk, cheese, eggs, fresh meat, or fresh vegetables. Five milligrams of riboflavine a day for three days was found to heal the mouths almost magically. Prior to an exact determination of what was lacking, children in India were cured by addition of skimmed milk or yeast to their diet of parboiled rice.

Riboflavine is widely distributed in plants, but grains and seeds are less richly endowed with it than with thiamin. Leaves and stems contain small amounts, especially the tops of beets, mustard, turnips, and carrots (for once spinach falls a *little* behind). Apricots and tomatoes are good sources, and also beef, veal, and chicken, but not fish or pork. Brewer's yeast is the richest vegetable source. Of ordinary human foods, milk, eggs, and liver are undoubtedly the best sources of riboflavine. Volume for volume, skimmed milk is richer in riboflavine than is cream, but since the latter contains nearly all the vitamin A, whole milk is usually preferable.

NICOTINIC ACID AND PELLAGRA

Pellagra, mal-de-rosa, or "sunburn of spring" as the Italians euphemistically call it, is a disease almost universally

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associated with a diet in which white corn (maize) is the mainstay. One of the first theories about it was that it was a poisoning from spoiled corn. Then it was believed to be an infectious disease, either caused by a germ found in corn, or transmitted by insects in corn-growing regions. This idea was exploded by Dr. Goldberger, who demonstrated the immunity of well-fed people to the disease, even when exposed to it on all sides, and showed that such people failed to contract the disease from any sort of inoculations from pellagrins. There is no doubt, however, but that infectious diseases, especially of the alimentary canal, may be instrumental in precipitating a case of pellagra.

Pellagra is one of the modern curses of Egypt, and frequently breaks out, especially in spring, in many parts of Europe and Africa, but there is probably more pellagra at present in our own southern states than in any other place in the world. In the United States a total of over seven thousand deaths a year from pellagra is not an infrequent record. In some years there are more deaths from pellagra than from tuberculosis or malaria. The poverty-stricken share-croppers of the Mississippi valley, and negro laborers on cotton plantations throughout the southeast, have this disfiguring and disabling disease always with them. It rises and falls with the price of cotton, with the advent of local floods, droughts, and malaria epidemics, and with the rotation of the seasons, for all these factors are concerned in the ability of these people to add to their basic diet of corn, molasses, salt pork, and coffee. In the summer they usually piece out their meals with a few fresh greens, water-melons, and black-eyed peas, but in lean years the winter menu consists of corn for breakfast, maize for lunch, and hominy for supper, with an occasional catfish or swamp rabbit to break the everyday routine. Although many chil-

dren and adults of both sexes suffer from the disease, pregnant women and nursing mothers suffer most. In localities which are only mildly afflicted the disease appears year after year in the spring to disappear later, but each recurring attack in an individual seems to leave a permanent lowering of his resistance, both to this and to other diseases.

The disease begins with loss of weight and waning strength, together with vague grumbling complaints, poor appetite, and fretful disposition. Later burning sensations appear in the mouth, in which the mucous membrane becomes fiery red, swollen, and fissured, so that swallowing is an ordeal. The skin is marked by red, rough, scaly areas which burn and itch, and ultimately acquires the parchment-like texture of a mummy's skin. These red areas have a strange symmetry on the two sides of the body, and most commonly appear on the parts exposed to light—ugly, painful patches on the backs of the hands, on the tops of the feet, in necklace formations, and as “butterfly wings” on the cheeks. The digestive system is upset also; the mucous membrane, especially of the colon, becomes red, thick, and congested, and dyspepsia, diarrhea, nausea, and vomiting are common. There are nervous symptoms too—muscular cramps, tremors, and a characteristic mental condition of melancholia, lethargy, and stupor; in severe cases hallucinations and delirium make the sufferers quite irrational. The lesions of the nervous system are similar to those of beri-beri, but occur mainly in the central nervous system while those of beri-beri are more marked in the peripheral parts. Undoubtedly, however, nearly every case of pellagra is complicated by some degree of deficiency in vitamin B₁ as well. The majority of pellagrins have anemia to add to their burden of discomforts.

Alcoholics very often suffer from pellagra as well as

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neuritis, and presumably for the same reason—lack of interest in non-alcoholic foods. There is a strong suspicion that sprue is another manifestation of the same deficiency as pellagra, complicated by infection with a yeast-like fungus; sore mouth, indigestion, diarrhea, and progressive anemia and wasting are the outstanding symptoms.

Years ago Dr. Goldberger observed that people who developed pellagra had poor diets, lacking particularly in fresh meat, eggs, and milk, and that if these and fresh vegetables were added to their bill of fare, pellagra could be prevented and cured. As noted above, the pellagra-preventing food factor was long ago known to be hidden somewhere in the vitamin G complex, but it was not until 1935 that it was clearly recognized as distinct from either riboflavine or B₆. Just two years ago (1937) the industrious group of nutrition workers at the University of Wisconsin, headed by Dr. Elvehjem, found that nicotinic acid would cure black-tongue in dogs. Since then it has been tried on human pellagra cases with dramatic success. Into the hospital of Duke University Medical School was brought a man who had suffered from pellagra for fifteen years, emaciated and dried up, covered with skin sores, mouth and tongue fiery red and swollen so he could barely swallow, mentally confused, diarrheic—a pretty thorough physical and mental wreck. He was given injections of 60 milligrams of nicotinic acid daily for eight days. His appearance was improved within twenty-four hours and his mind in forty-eight; in six days he had fully recovered his wits, and in twelve days his skin was normal—all by 10 cents' worth of nicotinic acid! To a Cincinnati hospital was brought an old skin-and-bone negress, mentally confused and semi-stuporous, unable to swallow or even to stand up, and expected to die. After three days of nicotinic acid treatment

her mouth became normal and she could eat. After a few weeks of building-up in the hospital she was discharged well enough to walk several miles to her home. Another case with badly inflamed mouth and vagina, skin sores, paralyzed legs, and scrambled mind, was dismissed a well woman in five weeks.

Nicotinic acid is an oxidation product of nicotine, but is about a thousand times less toxic. In the doses so far used in human treatments (60 milligrams a day by injection, or up to 1 gram a day by mouth), it produces no symptoms except a brief flushing and a little itching and tingling of the sore areas of skin and mucous membranes. Whether or not any nicotinic acid is obtained from smoking or chewing tobacco is doubtful. It is a substance found widely distributed in Nature in both plants and animals, and like thiamin is probably necessary to both.

Nicotinic acid is a durable substance, not destroyed by heat, ordinary acids, or alkalis, nor by exposure to air, so it is not likely to be injured by ordinary methods of food preparation. Most leaves contain it, but its distribution in grains and tubers is very irregular. It has recently been found that when rootlets are isolated from their parent plants and cultured in a nutrient solution of glucose and salts, they require traces of nicotinic acid as well as thiamin for continued growth. It has also been shown that cut tobacco leaves with their cut ends in a weak nicotinic acid solution absorb more water, live longer without wilting, and make much more nicotine than those in plain water. If this turns out to be generally true for cut stems and flowers, nicotinic acid may prove to be a boon to florists as well as to pellagrins.

The foods which have been found most effective in preventing or curing pellagra, and therefore presumably con-

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tain most nicotinic acid, are red meat, fish, liver, eggs, peanuts, and most greens. Wheat germ is also well supplied, but oats and corn have practically none, and beans and peas very little. Milk is not a very good source, and for once the good old Irish potato also fails to come to the rescue. Dried brewer's yeast is the richest natural source, and since it contains *all* members of the B complex is particularly valuable both in prevention and treatment of pellagra. One ounce daily is usually adequate for treatment.

In the past, attempts have been made by the Public Health Service, Red Cross, and other Good Samaritan agencies, to relieve the suffering in pellagra outbreaks by supplying meat, fish, eggs, greens, and other good foods, but the expense has limited the accomplishments. Much good missionary work has been done in educating people in pellagrous areas to supplement their meager diets, if only with catfish, rabbits, and dandelion greens.

Now, however, the possibility looms of abolishing or at least alleviating pellagra wholesale by the simple expedient of adding a trace of nicotinic acid to the table salt, as for years we have been adding iodine in goiterous areas. The first large-scale use of nicotinic acid for the alleviation of human suffering was in 1938, when American scientists sent a large shipment of it to Spain to relieve 40,000 people suffering from pellagra in Madrid. It is hardly to be expected that pellagrins can often be made entirely well by the use of nicotinic acid alone, for the poor diet which deprived them of this vitamin is almost certain to have deprived them of others as well, particularly thiamin. Nevertheless, with the most severe deficiency rectified, the improvement in digestion and absorption may go far towards alleviating the other deficiencies. Meanwhile educational efforts can be directed towards the establishment of small vegetable

gardens, and the raising of more cows and chickens. Since enough nicotinic acid to cure the symptoms of uncomplicated pellagra can be obtained from a drugstore for little more than the cost of a dozen aspirin tablets, and it is harmless in ordinary doses, there seems to be ample justification for its widespread use in pellagra outbreaks. What this may eventually mean in prevention of human suffering and misery it is impossible yet to judge.