side. Investigation of the sample of quercitrin by ultraviolet absorption revealed a small quantity of quercetin. As little as 4–5 per cent of quercetin would be sufficient to produce the degree of bacteriostasis observed in this experiment.

This is the first time that the flavonols have been shown to possess any antibiotic action. The discovery is especially timely, considering the present intensified interest in the subject of antibiotics derived from plants. The results also suggest the possibility of using rutin or the other flavonols to antagonize the hemorrhagic action of dicoumarol *in vivo*.

References

1. COUCH, J. F., and KREWSON, C. F. Mimeo. Circ. AIC-52, U. S. Dept. of Agriculture, July 1944.
2. COUCH, J. F., NAGHSKI, J., and KREWSON, C. F. *Science*, 1946, **103**, 197.
3. GOTH, A. *Science*, 1945, **101**, 383.
4. GRIFFITH, J. Q., JR., COUCH, J. F., and LINDAUER, M. A. *Proc. Soc. exp. Biol. Med.*, 1944, **55**, 228–229.
5. SCARBOROUGH, H. *Biochem. J.*, 1945, **39**, 271–278.

The Production of Experimental Pellagra by Adenine[1]

SIGWIN B. RASKA

Department of Pharmacology, Cornell University Medical College, New York City

Adenine, linked with other substances, is a constituent of many enzyme systems essential for life and, as a component of the nucleoproteins, is part of the structure of the cell. Many physiological processes are governed by catalysts containing adenine. Presumably, the concentration of free and bound adenine in tissues and body fluids is regulated by a mechanism which determines its formation and utilization, and such a regulation must be of importance to the animal economy.

An attempt was made to disturb this regulation by increasing the concentration of adenine, thereby interfering with the normal metabolism of adenine-containing substances, and of vitamins (especially of the B group), hormones, and enzymes.

Adenine[2] in the form of the free base alone or mixed with monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$) was given orally, in daily doses ranging from 400 to 500 mg. each, to three dogs over a period of from one to three weeks. The dogs (females) used for the experiments were fed before and during the experiment with K.F.S., Cero Meato (Kennel Food Supply Company, Fairfield, Connecticut), and with Red Heart, Diet B (John Morrell Company, Ottumwa, Iowa). Occasionally this diet was supplemented with milk.

The history of a dog which showed the characteristics common to all three animals given adenine supplemented with phosphate was as follows: Its weight was 11,260 grams; its age, about three years; time in the laboratory, seven months. The dog was given 400 mg. of adenine and 400 mg. of monobasic sodium phosphate daily in capsules by mouth. Loss of appetite was observed after the second day, and the dog became apathetic. On the fifth day the animal refused all food but continued to take water. The fur looked unkempt, and loss of hair was apparent. The systolic pressure was about 30–35 mm. Hg. above the values found during the control period. On the seventh day along the inner side of the cheeks and the inner upper lips areas of redness were present, stippled with false membrane and disseminated pustules. The tongue was pale grey, and the first quarter of the anterior portion had a brownish-grey appearance. A foul odor from the mouth was evident. The gums bled easily on slight pressure, especially near the alveolar arches of the teeth. Bilaterally, about two inches back from the tip of the tongue on the lateral inferior portion, inflamed areas, about one-half inch long and one-quarter inch wide, were present. The dog vomited occasionally. The systolic pressure was 25 mm. Hg. above the average value for the normal period. At the time of the last dose, given on the ninth day, a marked skin rash was evident, the mouth had a very strong odor, and the entire mouth and pharynx were inflamed. Areas of one-fourth to one-half inch in diameter, covered by a yellowish or yellowish-grey exudate, were present on the inner lips and cheeks, especially at the angle and on the floor of the mouth. Slight pressure on the gums, inner lips, and cheeks produced bleeding. The red line extending along the alveolar arches of the teeth had become a deeper red, and the inflamed areas on the lateral inferior portion of the tongue were covered with an exudate. The tongue had darkened, and the brownish-grey appearance of the anterior-superior portion had extended posteriorly to about two-thirds of its length. The remainder of the tongue was dark grey. The portion close to the tip was almost black and markedly atrophied. Drooling from the mouth was continuous, and the saliva contained some blood. The weakness of the hind legs was pronounced, and the dog staggered when it walked. The cornea of the eye was opaque, giving the iris a spotted, cloudy appearance. The sclera showed marked vascularization. On the margins of the eyelids a yellowish, thick secretion accumulated, causing the lids to adhere.

During the following days the weakness of the animal increased rapidly, and the blood pressure dropped below normal. Voluntary control of the tongue seemed to be almost completely lost. There was an increase in the number and severity of the inflammatory lesions in the mouth and pharynx. Occasionally the dog vomited small amounts of a bloody fluid. The day before the animal died 50 cc. of warm milk was given by stomach tube but was not retained. Death occurred on the 14th day of the experiment, at which time the animal weighed 7,170 grams. The total amount each of adenine and monobasic sodium phosphate given was 3.6 grams. Gross autopsy findings included: alopecia, emaciation, glossitis, gingivitis, stomatitis, congested liver, marked submucosal hemorrhages in the duodenum and marked congestion in the jejunum and ileum, yellowish-grey mottling of the entire surface of the kidney, hemorrhages in the medulla, and bulging of the cut surface.

Two dogs were given a daily dose of 300 mg. of adenine (free base) alone for a period of 21 days. The above-described

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[2] The adenine used in these experiments was supplied by Hoffmann-LaRoche, Inc., through the kindness of Dr. J. A. Aeschlimann.

signs and symptoms did not develop as fast as when phosphate was added. In addition, these dogs showed spasticity of the jaw muscles and extremities. At autopsy there were, in addition, hemorrhages in the esophagus, more extensive hemorrhages in the small intestines which contained digested blood, hemorrhages in the colon, and slight edema in the walls of the gastrointestinal tract.

Similar experiments were done with young albino rats. Adenine alone (0.5 or 1.0 per cent) or adenine plus phosphate (0.5 or 3.0 per cent) was added to the normal diet. At autopsy the kidneys showed a marked increase in size and weight. The entire surface appeared greyish mottled and hemorrhagic. The cut surface bulged, and the medulla was usually hemorrhagic.

The syndrome produced by adenine points to multiple avitaminosis. It shows all the symptoms described in experimental pellagra in dogs (black tongue). The opalescence of the cornea, the spasticity, and the ataxia observed are characteristic of riboflavin and vitamin A deficiency.

Adenine, or its metabolites, probably produced the syndrome by combining with constituents of the vitamins or their precursors, thus preventing their utilization in the animal. An interference with the formation and activity of alloxazine adenine dinucleotide, of the phosphopyridine dinucleotides (coenzymes I and II), and of nucleoproteins can be assumed. It is of interest to note that a rise in blood pressure resulted and that autopsy revealed extensive damage to the kidney.

These experiments demonstrate the existence of a direct relationship between purine metabolism and avitaminosis. A disturbance of the former may cause changes characteristic of various avitaminoses under dietary conditions which provide for normal vitamin requirements.

If the mechanism demonstrated in these experiments is applicable to human beings, the occurrence of pellagra, which is by far the most frequent variety of avitaminosis occurring in North America, might be reduced and the treatment aided by the elimination of foods containing adenine in a form producing the multiple avitaminosis. To that end the adenine content of certain foods will be determined.

These experiments are being continued and extended to other purines and purine derivatives. A detailed report, including the microscopic findings, will be published elsewhere.

Elasticity of the Aortic Wall

ALLEN L. KING

Department of Physics, Dartmouth College

The rubber-like characteristics of the aortic wall (*4, 11*) suggest that the wall material is essentially elastomeric. On applying the general theory for ideal elastomers (*5*), a relation is obtained between relative volume and fluid pressure within a cylindrical tube (*7*). Some data by Hallock and Benson (*3*) on segments of the descending human aorta for several age groups were analyzed by means of this relation. In it, the *effective* thickness, e_o, was treated as an adjustable parameter and computed for each age group. As anticipated, these values of e_o were smaller than actual thicknesses, such as measured by Krafka (*8*) on strips of aortas. It was suggested, however, that part of this discrepancy is due to a thickening of the aortic wall when peripheral chains are cut. That thickening on cutting does occur was pointed out recently by Remington, Hamilton, and Dow (*9*). Segments of canine aortas were found to decrease in length by as much as 30 per cent on removal (*10*), probably in this case due to a shortening of the longitudinal chains. In general, then, intact aortic walls are thinner and less firm than the removed segments.

In their discussion of aortic size, Bazett, Cotton, Laplace, and Scott (*1*) use values of the ratio of thickness to internal radius of undistended aortas as a function of age which were computed from data obtained by Kani (*6*). The estimated error in Kani's measurements, however, is greater than the apparent decrease of the ratio with age as reported by Bazett and co-workers for aortas. It is interesting to note that Kani's values for thoracic aortas yield a ratio of thickness to *external* diameter of 0.088 for the thinnest parts and 0.095 for the thickest parts, with a maximum variation with age of ± 0.008, only half the estimated average deviation of measurements for any one age group. The corresponding ratio, e_o/d_o, from the results found in Table 1 (*7*) are given below:

RATIO e_o/d_o FOR SEVERAL AGE GROUPS

Age group	20–24	29–31	36–42	47–52	71–78
e_o/d_o	0.094	0.081	0.077	0.073	0.052

The general decrease in the ratio, e_o/d_o, beyond the age of 20 years suggests that accumulating collagenous fibers and other deposits in the aortic tissues, along with the enlargement of the vessel, cause a thinning out of the elastomeric constituents. Apparently the ratio of actual thickness to diameter remains nearly constant at approximately 0.09, so that by the 75th year almost 50 per cent of the aortic wall is effectively non-elastomeric. On the other hand, the product, $e_o d_o$, is constant at 15 mm.^{2} to within an average deviation of 0.2 mm.^{2} over the age range of 20–80 years, as though the materials within the vessel wall that render it elastic really do not disappear but, rather, become more thinly dispersed with time (*7*). Elastin and similar constituents of blood vessel walls are relatively stable substances (*2*).

From this analysis of aortas the aging process appears, at least in part, to consist of a gradual, effective shortening of molecular chains within the aortic wall. Such an effect can take place either by the establishment of cross-linkages between chains or by introducing fix-points in the form of collagenous fibers and fatty aggregates.

References

1. BAZETT, H. C., COTTON, F. S., LAPLACE, L. B., and SCOTT, J. C. *Amer. J. Physiol.*, 1935, **113**, 328.
2. COWDRY, E. V. *A textbook of histology*. (2nd ed.) Philadelphia: Lea and Febiger, 1938. P. 132.
3. HALLOCK, P., and BENSON, I. C. *J. clin. Invest.*, 1937, **16**, 595.
4. HAMILTON, W. F., REMINGTON, J. W., and DOW, P. *Amer. J. Physiol.*, 1945, **144**, 521.
5. JAMES, H. M., and GUTH, E. *J. Chem. Phys.*, 1943, **11**, 455; KING, A. L. *Amer. J. Phys.*, 1946, **14**, 28.
6. KANI, I. *Virchow's Arch.*, 1910, **201**, 45.
7. KING, A. L. *J. appl. Phys.*, 1946, **17**, 501.
8. KRAFKA, J. *Arch. Path.*, 1940, **29**, 303.
9. REMINGTON, J. W., HAMILTON, W. F., and DOW, P. *Amer. J. Physiol.*, 1945, **144**, 536.
10. REMINGTON, J. W., and HAMILTON, W. F. *Amer. J. Physiol.*, 1945, **144**, 546.
11. ROY, C. S. *Foster's J. Physiol.*, 1880, **3**, 125.