

animals to maintain a normal acid-base equilibrium of the blood and to eliminate phenolsulphanephthalein.

Structural modification associated with the ageing process which may or may not be designated disease, has resulted in the stabilization of a fundamental equilibrium of the animal organism as the animal relates itself to its normal environment and to an abnormal environment brought about by the introduction of a chemical body foreign to its tissues.

Summary. Twenty-three senile dogs showing varying degrees of glomerular injury and at the same time a fairly diffuse change in the type of epithelium in the proximal segment of the renal nephron from a normal order of cuboidal cell to one of a flattened, less spe-

cialized type of cell when subjected to the anesthetic action of chloroform for 45 minutes fail to show, as the result of the use of this body, a reduction in the elimination of phenolsulphanephthalein, or a reduction in the reserve alkali of the blood from that value which these animals have established as their pathological normal. In a group of 29 control senile animals, with a normal urine, both chemically and microscopically, with the same order of change in the glomeruli but with, in general, a normal order of cytological structure in the proximal segment of the renal nephron when anesthetized for 45 minutes with chloroform show a marked decrease in the elimination of phenolsulphanephthalein and a reduction in the reserve alkali of the blood.

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Effect of Rutin on Increased Capillary Fragility in Man.

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Rutin is, like hesperidin, a flavone glucoside, and the two are very similar in structural arrangement. The chemical formula of rutin is $C_{27}H_{30}O_{16} \cdot 3H_2O$. Hesperidin has been shown by Szent-Györgyi and others¹ to have a beneficial effect on abnormally fragile capillaries, at least in certain cases. It seemed possible that rutin might have a similar effect. So far as we know, no studies have been reported previously in which rutin has been given to man.

Rutin is a constituent of a variety of plants,

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¹ Armentáno, L., Bensáth, A., Béres, T., Rusznyák, I., and Szent-Györgyi, A., *Deutsche med. Wchnschr.*, 1936, **62**, 1325.

² Sando, C. E., and Lloyd, J. U., *J. Biol. Chem.*, 1924, **58**, 737.

including tobacco, garden rue, forsythia, elder flowers, and violets. That used in this study was extracted from tobacco by essentially the same process described by Sando and Lloyd.² It had the proper melting point, and its purity and identity were confirmed by carbon and hydrogen determinations and hydrolysis by sulfuric acid to quercetin, dextrose, and rhamnose. The tobacco used was of the flue-cured type, of high quality, cured but not aged or fermented. Lower grades of flue-cured tobacco, the stems of flue-cured tobacco, and air-cured tobacco of any grade, were found to yield little or no rutin.

Rutin was given to 14 patients with hypertension who were attending the cardiac clinic of this hospital. The patients were chosen because they showed an increased capillary fragility, as measured by the Petechial Index of Gothlin.³ The substance was given by

³ Ahlborg, N. G., and Brante, G., *Act. Med. Scandin.*, 1940, **104**, 527.

mouth in capsules, starting with 20 mg twice a day and, usually, increasing to 3 times a day in a few weeks. Measurement of the Gothlin Index was repeated every 3 or 4 weeks, not oftener, because Gothlin had pointed out that a negative test is only significant if an interval of at least 3 weeks had elapsed since the previous test. Two of the 14 subjects were receiving potassium thiocyanate by mouth at the time the study was begun, and this was continued.

Results. In no case did any toxic effect develop that could be attributed to the rutin. One patient died of a stroke 2 weeks after beginning the medication. Two other patients did not return for adequate follow-up. However, 11 patients were followed for a period varying between 12 and 16 months. Capillary fragility became normal in 8 of these

within 2 months of beginning medication, while in 3 it remained increased. One of the subjects in whom the fragility remained high developed a hemiplegia 4 months after beginning medication, and is reported to have died. No complication developed during the period of observation in the remaining 10 subjects, nor was there any significant change in blood pressure. Two subjects stopped taking the rutin after the capillary fragility had returned to normal. Within 6 weeks the capillary fragility was again increased. Rutin was resumed, and when the capillary fragility was tested a month later, it was again normal.

Conclusion. At least in certain cases, rutin appears to have the property of decreasing capillary fragility in subjects in whom this fragility is initially increased. In this effect it resembles hesperidin.

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Further Observations upon the Protracted Effect of Alpha-tocopherol Administered to Nursing Rats.*

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In a previous paper,¹ it was shown that a single dose of 0.5-5.0 mg of alpha-tocopherol administered on the 15th day of life to rats born of mothers on an E-deficient diet, and maintained after weaning upon vitamin E low diet, produced a significant delay in post-pubertal degeneration of the testis. Similar doses given on the 5th day, or on the 28-30th day, were less effective than when given on the 15th day.

This paper is concerned with the effect of larger single doses, either given to the young directly, or through the mother's milk.

Experiment I. The mother was a third generation rat on E-deficient diet, 10 mg of alpha-tocopherol acetate having been given

at the beginning of each pregnancy. Litter H₂ was the second litter; the first litter of 7 young did not survive 4 days. The young of H₂ were given 1 drop (25.6 mg each) of alpha-tocopherol acetate on the 15th day of lactation. Semi-castration was performed when they were 107 days old, and they were killed on the 182nd day. Repeated fertility tests were made by mating the rats with females which had been kept on a stock diet. During the mating period, male and female had access only to vitamin E-deficient diet. The birth of a litter was considered a positive test.

Experiment II. Each suckling rat of a second litter was given 51.2 mg of alpha-tocopherol acetate on the 15th day. The mother was again a third generation rat on E-deficient diet. The results are summarized in Table II.

From previous data, it has been found that

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¹ Kaunitz, H., Pappenheimer, A. M., and Schogoleff, C., *Am. J. Path.*, 1944, **20**, 247.