

exposing virus was of the same strain as that used for vaccination, but consisted of the chorio-allantoic membrane which represents a greater concentration of virus than the entire embryo vaccine. The artificially exposed chickens were given three inspections at weekly intervals for lesions of fowl pox following exposure. Results of the exposure are noted in Table I.

Out of the 71, 3 susceptible birds were

encountered. These were from the same flock. Ten unvaccinated control birds simultaneously exposed to the challenging virus proved susceptible. Though the number of birds included in this observation is too small to permit conclusion, it appears that a large proportion, 95.7%, of this group immunized with entire embryo vaccine proved immune one year after vaccination.

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Relation of Changes in Proximal Segment of Renal Nephron to Maintenance of Acid Base Equilibrium.*

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In a previous publication¹ in which consideration was taken of the stability of the acid-base equilibrium of the blood in animals falling in different age periods, the observation was made that in a group of senile animals varying in age from 9-19 years, 6 animals showed chemical evidence of renal dysfunction in which this equilibrium was stabilized against the influence of a period of anesthesia from chloroform lasting for 45 minutes. Other members of this group (Group III) of senile animals which gave no chemical evidence of a renal injury failed to show this factor of resistance to the action of the anesthetic body. Further studies in senile animals have strengthened this observation by an investigation of 23 additional dogs that gave evidence of their ability to maintain what they had established as their normal acid-base equilibrium when this fundamental balance was subjected to an influence which in other senile animals and in dogs of younger age periods resulted in a depletion of the alkali reserve of the blood.

The control group of animals for this study is represented by 29 senile dogs that have

had normal urines both chemically and microscopically, an average elimination of phenol-sulphanephthalein of 38% in an hour period and a normal alkali reserve of the blood which varied between 8.05-8.15. Kidney tissue was removed from 4 of these animals under local anesthesia supplemented by nitrous oxide-oxygen. Such tissue has shown histologically unevenly distributed evidence of a chronic glomerular injury without any cytological evidence of epithelial participation in this process. The epithelium of the nephron in its different segments was of normal configuration. The brush border of the cuboidal cells in the proximal convoluted segment remained intact. In these 4 dogs and in the other members of the senile group of controls that gave no chemical evidence of renal disease the use of chloroform for 45 minutes resulted in an edema of the epithelium in the proximal convoluted segment, more rarely vacuolation and fatty degeneration and a disappearance of the brush border of these cells. Associated with such cytological changes in this epithelium there have occurred two modifications in renal function: a rapid reduction in the reserve alkali of the blood to readings as low as 7.75, a delay or inability on the part of the animals to restore this equilibrium and a reduction to as low as 5%

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¹ MacNider, Wm. deB., *PROC. SOC. EXP. BIOL. AND MED.*, 1943, **53**, 1.

in the elimination of phenolsulphanephthalein.

In contrast with these control animals, 23 senile dogs showing chemical evidence of renal dysfunction have been studied by employing a similar experimental procedure. From 4 of these dogs biopsy material was obtained from the kidney by the method which has been outlined. This tissue has also shown a diffuse but unevenly distributed glomerular injury. The order of change has been similar to that for the control senile animals that gave no chemical evidence of renal disease. It is impossible to evaluate comparatively either the severity or the functional significance of the glomerular injury in the two groups of animals. The essential cytological difference in the kidneys as a whole is that in those senile animals which manifested evidence of renal disease there has developed a change in the morphology of the epithelium lining the proximal convoluted segment of the nephron from the normal cuboidal type of cell with a brush border to an epithelium without this specialization and which is imperfectly differentiated into cell units. Such epithelial tissue is of a low, flattened order with prominent deeply staining nuclei and a cytoplasm which stains evenly and intensely. Functionally such animals have established as their pathological normal an alkali reserve of the blood which is below the normal average for such a value: 8.0-7.9. The elimination of phenolsulphanephthalein in an hour period has shown a reduction varying from 18-29%. When such senile animals are subjected to an anesthesia from chloroform for 45 minutes the acid-base equilibrium with 2 exceptions has remained uninfluenced by the anesthetic body. In the 2 exceptions noted the reserve alkali has been reduced from the low normal of 8.0 to 7.9. The elimination of phenolsulphanephthalein in an hour period following the anesthesia has shown a greater degree of variation. In 19 of the dogs the percentage elimination of this dye was unchanged. In 4 of the animals the output was reduced from a maximum of 38% to as low as 12%. Two of these animals with an elimination of phenolsulphanephthalein of 12% and of 17% have been referred to as animals in which the reserve alkali of the blood was also depleted by the anesthetic.

The histological study of the kidneys of these 23 senile animals that showed resistance to chloroform by maintaining the acid-base equilibrium of the blood and which had continued to eliminate phenolsulphanephthalein in amounts equivalent to the preanesthetic percentage demonstrated the inability of the anesthetic to induce injury to the atypical order of epithelium which had made its appearance in the proximal convoluted segment of the nephron. By employing such histological criteria it is impossible to state whether or not the use of the anesthetic altered functionally the effectiveness of the glomeruli. There has been no cytological evidence of such a superimposed acute injury.

In past years this same order of fixed tissue cell resistance associated with morphological change in cell type has been observed for the kidney² and liver³ against secondary injury from uranium nitrate and also for the liver⁴ to the hepatotoxic action of chloroform after a repair process had developed which was associated with a shift in cell type. Furthermore, in certain senile dogs⁵ there has been observed to occur, associated with the aging process, a change in form of the epithelium of this organ from the usual polyhedral type of cell to an order of cell or syncytial structure definitely comparable to the altered type of cell which has been described in this discussion as occurring in the proximal convolution of the nephron in the animals which manifested the same type of resistance to chloroform.

From the comparative study of the 2 groups of senile dogs it would appear that the group which has shown evidence of functional renal impairment and in addition to the chronic glomerular changes common to both groups has shown an alteration in the type of epithelium in the proximal convolution of the nephron, that there is a relationship between this latter change and the ability of such

² MacNider, Wm. deB., *J. Exp. Med.*, 1929, **49**, 411.

³ MacNider, Wm. DeB., *J. Pharm. and Exp. Therap.*, 1936, **56**, 359.

⁴ MacNider, Wm. deB., *J. Pharm. and Exp. Therap.*, 1936, **56**, 373.

⁵ MacNider, Wm. deB., *J. Pharm. and Exp. Therap.*, 1936, **56**, 383.

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.