be toxic, as e.g. was shown by VAN OSTERHOUT's soil-experiments. Addition of $CaCl_2$-solutions to the otherwise fairly favourable soil was injurious to the cultivated plants; addition of KCl-solutions was not. VAN OSTERHOUT interprets this by pointing out that through the addition of Calcium the relation of the two metals departs more and more from the optimal whereas it approximates the optimal relation through the addition of Potassium.

Reverting to our broom we see that relative to the soil of the Land van Diepenhorst the calcium-content of the soil of the Central-dunes rises from 0.015 % to 0.90%, i.e. ± 60 times the original value. On the contrary there is no appreciable total increment of the potassium-, and the sodium-salt-content: in the Central-dunes this was 0.08 %, in the Land van Diepenhorst 0.06 %.

The relation in the Western and Central-dunes has been largely modified, so that the equilibrium for the true calcifuge plants, such as Sarothamnus, has been disturbed. The view is favoured by the fact that calcifuge-plants, such as Castanea vesca, can be cultivated in calcium-rich soil, provided the soil is of itself potassium-rich [1]), or potassium is added to it, SCHIMPER [2]) maintained that calcium inhibited the absorption of ironsalts, and that addition of ironsalt-solution to calcium-rich soil removed the excited chlorosis. By others, among whom SIDORINE [3]), this was however refuted and ascribed to the alkalinity of the nutrient solution that had been used.

For Magnesium LOEW [4]) asserted that a certain ratio of Ca and Mg is required for a satisfactory development, which, however, has been negatived by Russian and American writers [5]) on the science of manuring.

With the method for soil-examination adopted by me I found in both soils only traces of magnesium; I, therefore, refrain from giving my opinion about this question, which may be solved through subsequent experiments, which I purpose to perform with the Sarothamnus by cultivating it on calcium-richer soil to which various salts will be added. This however is a time-consuming undertaking; for the time being experiments with water-cultures of buck-wheat were indicative of the great importance of the antagonism of the salts of univalent and bivalent metals in the problem of calcifuge plants.

1) ARNOLD ENGLER, Ber. Schweizer. bot. Ges. 1901.
2) SCHIMPER, Pflanzengeographie. 1908.
3) SIDORIN. Ergebn. Landw. Stat. Moskou 1916..
4) LOEW. Bull. Agric. Coll. Tokyo 1902. Die Lehre vom Kalkfactor. Berlin 1914.
5) A. DOJARENKO Journ. f. experim. Landwirtschaft 1903, F. A. WATT Journ. agr. research 1916.

Physiology. — *"On the Pharmacological Action of Isoamylhydrocuprein (eukupin) and Isoctyl hydrocuprein (vuzin)"* By Prof. R. MAGNUS and U. G. BIJLSMA.

(Communicated at the meeting of April 23, 1920).

Of late years especially three compounds out of a series of hydrocuprein-derivatives, which had been examined by MORGENROTH and his pupils on their antiseptic action in vitro and in vivo, have been applied in therapeutics. These researchers had namely discovered that the alkylated hydrocuprein-derivatives were strong antiseptics every member of this series having a specific affinity for certain micro-organisms.

Thus ethylhydrocuprein counteracted especially pneumococci; isoamylhydrocuprein antagonized diphteria bacilli, bacilli of malignant edema and pyogenous cocci; isoctyl hydrocuprein neutralized the effect of bacilli of malignant edema and pyogenous cocci still more than isoamylhydrocuprein did (in vitro; in vivo they showed little difference). These three substances were given the commercial names, respectively of optochin, eukupin and vuzin.

As most commonly happens with the products of chemo-terapeutic researches, also these three substances were applied to patients or to men under suspicion of being infected, before pharmacological examination had sufficiently established their effects upon the mammal. Indeed, with respect to optochin inquiries were made later on, but hardly anything was effected in this direction for eukupin and vuzin. In order to meet this deficiency as far as possible, we have examined pharmacologically the double-hydrochloric acid salts of the latter two substances, which were put at our disposal through the kindness of Prof. MORGENROTH (Berlin). Before long these experiments will be published [1]) in extenso in another place; for the present we are able to give a concise report of our results, in which eukupin and vuzin stand for the double hydrochloric acid salts.

1. The pharmacological action of eukupin and vuzin (in the cases examined) agrees for the most part with that of quinine.

2. Eukupinae bihydrochloridum is soluble in distilled water to

1) For the bibliography we refer also to this detailed publication.

5%, vuzinal bihydrochloridum to 1% (5% solutions are clear again, concentrations between these values are turbid). In a physiological common-salt solution, Ringer-, or Tyrode-solution, turbidity practically exists in every concentration.

In serum eukupin-biHCl dissolves to 1 : 14000, vuzin-biHCl to 1 : 20000. When the solutions in serum are made to foam, the two substances are collected in a higher concentration in the foam than in the liquid. The foaming is diminished by the addition of much alkaloid-salt.

3. With subcutaneous injection the fatal dose for white mice per kg. body-weight is for eukupin : 300 mgr. and for vuzin : 200 mgr. So the toxicity of either substance, administered subcutaneously, is for mice two- or three-times greater than that of quinine.

The subcutaneous fatal dose for cats per kg. bodyweight, amounts to from 25 to 50 mgr. of eukupin, 200 mgr. of vuzin.

4. With slow intravenous injection the fatal dosage per kg. cat varies with the concentration of the alkaloid salt : in a 1% solution it amounts per kg. cat to about 13 mgr. of eukupin and about 15 mgr. of vuzin ; in 1‰ solution per kg. cat to 70 mgr. of eukupin (in one experiment, in which vagi intact) ; and 40—120 mgr. of vuzin (vagi intact or cut).

In the case of rabbits the intravenous fatal dosis of eukupin (in 1‰-solution) seemed to vary with the Nn.-vagi being unimpaired or cut through : it was per kg. rabbit with unimpaired vagi about 13 mgr., with vagi cut about 60 mgr. It appears from this that in the rabbit eukupin acts upon the vagus-center.

5. After subcutaneous injection of eukupin and vuzin cats die under a progressively increasing sopor. Large doses of eukupin cause a marked fall of temperature.

6. Subcutaneous injection of concentrated solutions (5%) of the two alkaloid-salts brings about local necrosis of the skin and the subcutaneous connective tissue.

7. Cleansed sheep's blood-corpuscles suspended in Ringer's solution, were hemolyzed through eukupin in a concentration of about 1 : 5000 through vuzin in a concentration of about 1 : 10000.

The number of red blood-corpuscles per mm^3 plays some influence upon the required concentration of the alkoloidsalts.

In the presence of serum the concentration of both substances, required for hemolysis, is about 1 : 1000.

8. Eukupin and Vuzin in 1 %-solution convert oxyhemoglobin into a brown colouring substance, which in an acid as well as in an alkalin solution shows in the absorption-spectrum spectroscopically as well as spectrographically a line in orange, right to the left of *D*, while the violet portion of the spectrum is shortened. The substance formed is decidedly not methemoglobin and not hematin.

9. On the frog's heart at the Straub-cannula eukupin acts with certainty deleteriously in a concentration of 1 : 50.000 (in RINGER) ; vuzin does so in a concentration of 1 : 150.000 (in RINGER). Either substance, in concentrations of 1 : 10.000 and higher, produces a standstill of the heart, eukupin a diastolic, vuzin a systolic standstill.

Serum, and red blood-corpuscles diminish the action of both substances on the frog's heart.

The cardiac muscle deprives the solutions of both substances.

The lesions to the frog's heart are little or not reversible.

10. The isolated mammalian heart perfused after LANGENDORFF is brought to a systolic standstill by either substance in concentrations of 1 : 10.000 in RINGER's-solution.

A solution of the two salts in undiluted mammalian blood lessens their activity.

The lesion to the heart cannot be restored by washing out with RINGER's solution, very little with blood.

11. Eukupin causes the peripheral vessels of cold- and warm-blooded animals, separated from the central nervous system, to distend (smallest concentration 1 : 20.000) ; vuzin has under the same conditions a constrictive influence (smallest concentration 1 : 10.000).

12. Eukupin and vuzin most often constrict the pneumonic vessels ; quinine and quinidin distend them (smallest concentration about 1 : 20.000).

13. Eukupin and vuzin do not manifest a distinct action on the coronary vessels in the rabbit's heart perfused with RINGER's solution after LANGENDORFF. Eukupin widens the coronary vessels of the cat's heart perfused with blood after LANGENDORFF (vuzin not examined).

In the Starling-preparation (dog) modified after DUSSER DE BARENNE eukupin (1 : 90.000 in blood) caused a marked distension of the coronary vessels, vuzin (1 : 60.000 in blood) a smaller.

14. Intravenous injection of eukupin and vuzin causes lowering of the bloodpressure in cats and rabbits, in which process the following factors play a part :

a. weakening of the heart-muscle ;

b. distension of the coronary vessels (after eukupin stronger than after vuzin) ;

c. distension of the peripheral vessels (permanent after eukupin, transient after vuzin) ;

d. constriction of the bloodvessels of the lungs.

The bloodpressure regains entirely or partially the original height through the following factors:

a. lessening of the concentration in the blood;

b. increase of the output;

c. constriction of the peripheral vessels after the initial distension through vuzin.

15. Intravenous injection of vuzin lessens the action of intravenous adrenalin-injection on the rise of the blood-pressure; ultimately these injections do not yield any appreciable result.

16. Intravenous injection of vuzin lessens the effect of faradic vagus-stimulation on the heart.

17. In the isolated cat's lung perfused with undiluted blood vuzin causes constriction of the bronchi; eukupin, quinine and quinidin cause distension of the bronchial tubes (concentrations about 1 : 20,000).

18. Eukupin, vuzin and quinine nearly always inhibit the action of the isolated small intestine of the cat and the rabbit, they rarely stimulate it. The effect of quinine can be washed out; that of eukupin and vuzin can not.

19. Eukupin, vuzin and quinine exerted in our experiments only an inhibitory influence upon the isolated uterus of the cat and the rabbit. Neither the quinine, nor the eukupin-action appeared to be reversible.

20. On application in 1 °/₀₀-solution for one minute to the rabbit's cornea eukupin and vuzin produce a transient total anaesthesia. 1 °/₀-solutions are very deleterious to the cornea.

21. When given in a 1 °/₀₀-solution, eukupin and vuzin bring about an interruption of the conduction in the sensitive ischiadicus-fibers of the frog (local application).

22. In a 1 °/₀-solution both salts cause a total interruption of the conduction in the N. ischiadicus of the frog (local application). This effect can be washed out in the case of either substance.

23. Eukupin and vuzin, injected intravenously in non-fatal dosis, do not influence the centres of the spinal cord of rabbits.

24. Eukupin elicits stimulation of the vagus-center in rabbits; vuzin does not affect the vagus-center in cats. (Compare N°. 4).

25. On intravenous administration both alkaloid salts produce stimulation of the respiratory center in cats and rabbits.

26. When the hindlegs of the frog in the Laewen-Trendelenburg preparation are perfused with eukupin and vuzin in Ringer's solution in small doses the result is increased lassitude, in larger doses decreased excitability of the muscles. In this process indirect excitability is influenced more than the direct. Quinine has a similar action. The action of vuzin is strongest, that of eukupin is weaker, that of quinine is weakest. In the strongest concentrations the three salts cause a total rigidity of the muscles. The action is only sparingly reversible through washing with Ringer's solution, a little more after quinine than after the other substances.

27. In the normal rabbit vuzin, injected subcutaneously in doses of 50 mgr. per k.g., causes a temporary fall of the temperature. Eukupin, on the other hand in the same dosage has no effect on the temperature of the normal rabbit.

28. After fever has been excited by injection of coliendotoxins + killed bacterium coli, both substances, like quinine, in a dosis of 25 mgr. per k.g. lower the temperature in the rabbit.

29. After subcutaneous and intramuscular injection eukupin and vuzin are resorbed only very slowly. Rests are found at the place of injection even after four days.

Of an intravenous injection of vuzin, in almost fatal dosis, about $^1/_7$ is still retained by the blood after 35 min., the rest is almost entirely to be found again in heart, liver, kidneys, adrenals, brains, spinal cord and muscles. After 24 hours only traces are to be found in these organs. Also with this intravenous injection no vuzin was found in the urine.

Thus it appears that vuzin is destroyed rapidly after intravenous injection.

30. In defibrinated blood vuzin is distributed over bloodcorpuscles and serum in such a way that in the corpuscles the concentration is from 7.7 to 16.6 times as high as in the serum.

31. Various organs (heart, liver, muscles) in vitro largely detach eukupin and vuzin from their solutions in Tyrode.

In vitro no abolition of the two salts by the named organs was demonstrable.

32. After subcutaneous injection of doses that just failed to be fatal neither of the alkaloids could be demonstrated in the urine of the cat and the rabbit.

33. The growth of Micrococcus tetragenus in 1 °/₀ glucose-broth is inhibited by eukupin in a concentration of about 1 : 150.000, by vuzin in a concentration of 1 : 300.000 or 1 : 500.000.

34. The antiseptic action of solutions of the two alkaloid-salts decreases largely after some days' standing.

35. Likewise the antiseptic action of the two substances decreases largely through dissolving in a physiological common-salt solution.

36. The presence of red blood-corpuscles in the fluid culture medium weakens the antiseptic influence of eukupin and of vuzin.

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