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Physiology. *"On the Electric Nebulae of Antipyretica."* By
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(Communicated in the meeting of February 23, 1918).

Two years ago¹⁾ one of us called attention to the excess of electrical charge, positive or negative, appearing when a solution of odorous substances in water is sprayed. Other publications on the same subject have appeared since²⁾. However, a superficial preliminary investigation showed at the very outset not only that odorous substances possess this remarkable property, but also that a number of other physiologically active, pure, chemical substances produce the same, though less appreciable electrical effect³⁾.

Nebular electricity is generated by odorous substances, saponins (odorous as well as inodorous), glycosides (most often slightly odorous), alkaloids (odorous as well as inodorous), antipyretica (odorous as well as inodorous), and a few more groups of other physiologically active substances that will be reported afterwards. In order to evolve the electrical phenomenon a substance, added to water, and sprayed with it, will have to satisfy some conditions, which seem to be:

- 1st. it should be soluble in water;
- 2nd. it should lower the surface-tension;
- 3^d. it should volatilise, when spread over a large evaporation area.

No electrical charge is evoked in any concentration by anorganic salts and acids, glycerin, sugars (provided they be pure), dextrin, lecithin, albumin, etc.

In the present communication we propose to discuss more in detail the electrical phenomenon of antipyretica, which we shall classify into three groups:

¹⁾ These Proceedings, Vol. 19 p. 44.

²⁾ Ibid. Vol. 19 p. 334, 351. Archives Neerlandaises de Physiologie t. 1. p. 347. E. L. BACKMAN. These Proc. Vol. 19 p. 943, PFLÜGER'S Archiv Bd. 168 p. 351; C. HUYER, De olfactologie van aniline en homologen. Diss. Utrecht 1917.

³⁾ These Proc. Vol. 19 p. 340, H. ZEEHUISEN, 3e Physiologendag, Dec. 1917. (Proc. not out yet. Vide Ned. Tijdschr. v. Geneesk. 1918).

- a. antipyretic alkaloids;
- b. salicylic acid and its derivatives;
- c. the other anodynes and the medicines that lower the temperature.

Group a. The antipyretic alkaloids are on the whole sparingly soluble, at the most up to $\frac{1}{1000}$ n. The surface tension is distinctly lowered by chinin, chinidin, cinchonin; it was not demonstrable in cinchonidin, chinamin, conchinamin. Volatility is undoubtedly a property of cinchonin (according to sublimation test) and of chinamin (in consequence of the loss of electrifying power subsequent to the suction of air). The saturated aqueous solution, sprayed under an overpressure of two atmospheres, distinctly electrifies a screen arranged in the way of the nebula at a distance of about 25 cm. The sign of this charge is positive (as in the case of most odorous substances) and the air round it and at some distance from it is charged negatively. Though clearly noticeable, the phenomenon falls behind that of the odorous substances.

Group b. Salicylic acid and its derivatives represent a group of chiefly crystalline substances, whose solubility differs much. Amongst them there are two that are completely insoluble, viz. salol and benzylsalicylate, and on that account have no or hardly any electrifying power. Of the remaining only salicylas chinini is soluble to less than $\frac{1}{1000}$ n, the others at least to 2.5 millinormal; some of the salts of salicylic acid are even extremely soluble in water. The lowering of the surface tension is on the whole slight, even absent in the case of the salts (after the trickling method); only with the liquid substances of this group and with aspirin is the lowering very distinct. Volatility is noticeable with salicylic acid, for it sublimates (consequently also with the salts of salicylic acid for they are dissociated in the dilute solutions), and also decidedly with the liquid representatives of the group (judging from the boiling point).

The intensity of the electrical phenomenon they evoke, varies very much. With the insoluble ones the charge, as has been said, is 0 or very near it; with the salicylic acid and the benzoic acid salts it is moderate, at the least 4 scale-divisions of our electroscope; with the others it is stronger, often even maximal, as with the typical odorous substances (camphor, alcohol, etc.).

The salicylic acid salts owe their electrifying power to the anion. The attending cation even lessens the charge of the nebula, probably because it is detrimental to the surface activity of the liquid.

As may be expected the consequence is that salicylic acid and salicylic acid salts determine the electrifying power of the nebula in a similar way, there being only a quantitative difference in such a sense that the salt produces a lower charge than the acid.

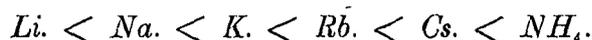
An intercomparison of the various concentrations of the acid, which is best expressed in a graphical way, shows that the optimum electrifying power of salicylic acid is located at about 1 millinormal; beyond it or below it the charge of the nebula is much weaker. Such an optimum is not only lowered, but also shifted by the coincidence of a cation, so that for salicylas natrius e.g. under the same conditions it is located in the 6 per-mille-concentration.

We have made an attempt to compare the univalent cations with regard to their capacity of shifting the optimum and of depressing the charge. When taking a 1 millinormal solution of the salicylic acid, the deflections of the electroscope will decrease proportionally through the addition of cations. The following table gives the factors by which the deflection of the electroscope, caused by the salicylic acid alone, must be divided in order to find the deflection that appears when adding a certain salt to the salicylic acid:

Factor by which the deflection of the electroscope is reduced, when spraying a mixture of 0,001 n. salicylic acid and the chloride of the subjoined alkalimetals, instead of spraying 0,001 n. salicylic acid alone.

Conc. of the added salt. solution.	Li	Na.	K.	Rb.	Cs.	NH ₄ .
0.01 n	∞	∞	∞			
0.005 n	9.6	10.1	∞	∞		
0.002 n	2.57	2.86	2.69	4.00		∞
0.001 n	1.68	2.27	1.95	2.36	2.90	4.3
0.0005 n	1.35	1.40	1.49	1.67	1.77	2.20
0.00025 n	1.05	1.14	1.30	1.40	1.42	1.50
0.000125 n		1.07		1.20		

It will be seen that the charge of the nebula decreases gradually from left to right. The factor reducing the deflection increases from Lithium to Ammonium.



which calls to mind the known lyotrope series. Our nebula is also

a colloidal system, consisting of the phase liquid (dispers) and gas (dispergent). On the surface of the droplets there is an electric potential, on the *bigger* droplets by which the charge on the screen is measured, it is negative. Of the other salicylic acid salts we had still at our disposal strontium- and bismuth-salt. They also possess a moderate electrifying power, just as sodiumbenzoate.

The esters of salicylic acid at our disposal: aspirin, novaspirin, diaspirin, the methylsalicylate and the spiroal, all yielded powerful charges.

Group c. The third group comprises three series: α the chinolin-derivatives, β the pyrazols, γ the paramidophenols. There is only one insoluble substance amongst them, all the rest are soluble and moreover crystalline.

For citrophen the lowering of the surface-tension could not be demonstrated. We also found that with most of the substances the surface-activity was inconsiderable. Only with euphorin, acetopyrin and kairin the lowering may be called significant. Slight volatility is generally noticeable if the evaporation area be large.

As regards the intensity of the electrical phenomenon it may be observed that the completely insoluble representative of group *c* does not yield a charge, which is in keeping with its insolubility; that the phenomenon occurs with moderate intensity in the case of pyramidon, phenacetin, and citrophen; that it is somewhat stronger with kairin, but extremely distinct with antipyryn, salipyryn, acetopyryn, tussol, antifebrin, and euphorin.

From the foregoing we may therefore conclude that all antipyretica, except those that are completely insoluble, yield the electrical phenomenon.

As has been set forth in previous publications, the electrical charge of a nebula is carried exclusively in the droplets it holds. Being sprayed under an overpressure of two atmospheres the fluid emerges from the nozzle of the sprayer in the shape of little drops. Of these drops the smaller ones are blown about and scattered in all directions. For odorous substances they are charged negatively. The bigger drops, which are charged positively, rush ahead in straight, divergent lines. When caught up at a proper distance, (for the antipyretica at 25 cm. from the sprayer) on an insulated screen, the latter will receive a positive charge that is pretty strong, though it is never so strong with antipyretica as with odorous substances (in aqueous solution).

In order to obtain normal results it is necessary to earth the sprayer. The amount of positive or negative charge present where the screen has been placed, may be largely affected by admixing cane-sugar or sodium chloride to the solution to be sprayed.

By the admixture of cane-sugar the charge on the screen is always raised, with the antipyretica extinction never occurs. The admixture of sugar is indifferent in the case of solutions of mesotan, tussol, and antifebrin. It goes without saying that in the like experiments due care should be taken that the sugar be perfectly pure, since an old sugar-solution is of itself electrifying.

The substances evolved under the circumstances can be removed from it only by filtration through animal charcoal (not so easily through extraction with absolute alcohol and subsequent cautious evaporation of the alcohol from the purified sugar left after filtration).

The effect of an admixture of sodium chloride is quite different. The concentration in which it takes place is of the greatest influence, as appears from the following table:

Factor of decreasing the charge of salicylic acid and salicylas natricus through various NaCl-concentrations.

NaCl sol. (conc.)	Salicylas Na. 0.00125n.	Salicylic acid 0.00125n
0.01 n.	∞	∞
0.005 n.	∞	10.1
0.0025 n.	4.2	4.6
0.00125 n.	2.1	2.4
0.000625 n.	1.8	1.8
0.0003125 n.	1.6	1.6

Seeing that even traces of sodium chloride modify the charge, it is essential to make certain beforehand that suitable water be used for solution. Distilled water cannot be recommended, since after standing for some days in a well rinsed bottle, it obtains of itself electrifying power (analogon of the old sugar solution). By shaking it for a considerable time with pure animal charcoal and by subsequently filtering it, distilled water can also be liberated from the electrifying admixture, which is volatile, for suction of air removes it in part at least.

The tapwater of the Utrecht Water Company being nearly free from

mineral salts we used it quite fresh (old tapwater also possesses electrifying power).

In cities with salt-rich tapwater the complication just described will have to be taken into account.

Physiologically the behaviour of the solutions is of interest when sodium chloride is admixed till a concentration of the latter of 0,9 % is reached.

It follows then that of

Group a. 4 obtain a higher electrifying power, 2 a lower, viz. chinamin and conchinamin.

Group b some are strengthened, others are weakened; salicylates, antipyrin and liquid derivatives are strengthened.

Group c. Antipyrins and chinolins are strengthened, urethans are weakened, and phenetidins remain unaltered.

No explanation of the sodium chloride effect has as yet been provided. Our experience with the salicylic acid salts points to a cation effect. To account for the fact we might also have recourse to the change of the surface tension in the droplets. Certain it is that the size of the droplets very much depends on the nature of the cation. The droplets of sprayed ammonium chlorid solution are much larger than those of sprayed sodium chloride solution (established ultra-microscopically).

For the rest in splitting the generally very complicate molecules all sorts of additions of electrical power may turn up.