ON THE PASSAGE OF BORIC ACID THROUGH THE SKIN BY OSMOSIS.

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INTRODUCTION.

Some years ago Dr. Edward H. Ochsner and I made a study of the action of boric acid when patients were treated for blood poisoning by means of compresses of boric acid solutions. The essential results were reported by Dr. Ochsner in a paper on "The treatment of septic infections of the extremities." In that investigation it was found that when aqueous solutions of boric acid, to which alcohol either had or had not been added, are applied to the skin of persons suffering from blood poisoning, the boric acid actually passes through the unbroken skin and makes its appearance in the urine in estimable quantities. The treatment consisted of applying a saturated aqueous solution of boric acid in the form of a large wet dressing to the affected part. This dressing was kept at body temperature, or what was more commonly done, 1 volume of 95 per cent alcohol was added to 3 volumes of the saturated aqueous solution of boric acid. The presence of the alcohol prevents the cold, clammy feeling which a large wet aqueous dressing causes when it is not kept warm. To keep such a purely aqueous dressing at body temperature, or a little above, for hours at a time would require constant attention on the part of the nurse. Various strengths of boric acid were tried in this research, but the best results were obtained when a saturated solution was used. This is what one would have expected since boric acid is but sparingly soluble, the saturated solution at ordinary temperatures containing only about 4 per cent. In all of the cases treated, the amount of

boric acid found in the urine was small. It very seldom was as much as 1 per cent, generally being only a few hundredths of a per cent, or at best 0.1 or 0.2 of a per cent. The boric acid was commonly found in the urine after an hour's treatment. The length of time required for the boric acid to make its appearance in the urine in detectable quantity was not a special object of the investigation, for that would naturally depend upon the area treated, the care used in cleansing the skin before putting on the compress, and keeping the latter warm and in perfect contact with the skin. The treatments were continued for 48 hours and the urine was examined from time to time for 46 hours after removing the compress. It was thus definitely established that boric acid is actually absorbed by the skin, and that it is eliminated by the kidneys, traces of boric acid being still found in the urine 46 hours after the topical application had ceased.

These investigations on the use of boric acid in the treatment of infections interested me in the experimental study of osmosis, and the results of the osmotic studies carried on were published in a series of papers from this laboratory, the basal one being entitled, "On the nature of the process of osmosis and osmotic pressure with observations concerning dialysis." In that paper it has been conclusively demonstrated by experiment that "whether osmosis will take place in a given case or not depends upon the specific nature of the septum and the liquids that bathe it; and if osmosis does occur, these factors also determine the direction of the main osmotic current and the magnitude of the osmotic pressure developed." All osmotic experiments made since the publication of that basal article have served to confirm this conclusion, which is also substantiated by the work of earlier investigators. To be sure, these osmotic experiments were performed with lifeless membranes, that is to say with dead animal or plant membranes on the one hand, or with inanimate artificial septa on the other.

In the course of my experimental osmotic work I found that not only boric acid but also urea, cane-sugar, sodium chloride, potassium chloride, lithium chloride, rubidium chloride, cesium chloride, sodium sulfate, and borax all pass through animal membranes such as the pericardium, urinary bladder, gall cyst,
stomach, intestine, aorta, and diaphragm of the hog, cow, or sheep; also through dead human skin. The latter was obtained from the dissecting room of the anatomical department and was taken from the outer wall of the abdomen. Osmotically it was found to make no difference in any of these cases as to which side of the dead membrane was presented toward the solution and which to the pure water. The substances passed through readily in either case. Moreover, all of the substances also passed through vegetable membranes such as apple skins, and the rinds of oranges, lemons, and grapefruit. In all of these experiments the procedure was quite simple, the septum being stretched over a suitable wooden frame so as to form a sort of cup to receive the solution, the outer side of the membrane being bathed with distilled water. However, as already stated, all of these membranes were dead and in the investigation of the treatment of infections by means of boric acid applications the membranes were, of course, alive.

After finishing the above mentioned work with Dr. Ochsner, I concluded to make some further investigations of the passage of dissolved substances, and particularly of boric acid, through perfectly normal living skin. It seemed to me highly desirable to carry on such experiments in order to ascertain whether substances other than boric acid actually pass through the living skin in estimable quantities or not, especially since it is commonly held that the latter is practically impermeable to non-corrosive substances brought into contact with it.

EXPERIMENTAL.

The experiments were performed in a simple manner. Both feet were washed with hot water and a little castile soap, thoroughly rinsed repeatedly with warm, distilled water and finally with 20 per cent alcohol. After being wiped with a clean cloth, they were then immersed to a depth just above the ankle in the solution to be tested. The latter was kept at 45°C. in a 5 gallon stoneware jar which served as the foot bath. The feet were kept resting but lightly, and not flatly, on the bottom of the jar, and they were also moved about occasionally. Samples of urine were taken from time to time, and analyzed. The spectroscope was employed in testing for lithium, cesium, rubidium, and
The entire urine was carefully evaporated to dryness and the residue acidified with concentrated hydrochloric acid before bringing it into the flame for the spectroscopic test.

The turmeric paper test was employed in testing the urine for boric acid, the entire sample of urine being made slightly alkaline with pure sodium bicarbonate evaporated to dryness and the residue ignited. The residue was then dissolved in a little water and acidified with concentrated hydrochloric acid. The turmeric paper was then dipped into this solution and dried on a large convex cover-glass on the water bath. The urine may also be acidified directly with concentrated hydrochloric acid, the turmeric paper dipped into the resulting solution and dried on the water bath. Only in this case, the red color developed by the paper has a somewhat darker shade, probably due to the coloring matters in the urine. If the turmeric paper is fresh and of good quality, the red color developed by the boric acid is quite bright and uniform, and the test may be used to make quantitative determinations of small amounts of boric acid. This fact was found early in the investigation. By making a 1 percent standard solution of boric acid in water and then preparing various lower strengths by appropriate dilutions, acidifying each of the latter with a definite amount of concentrated hydrochloric acid, dipping turmeric paper (2 by 4 cm. in size) into each of these dilutions, and drying the papers on the water bath, a color scale was obtained by means of which satisfactory quantitative estimations could be made. If the urine is made alkaline, evaporated, and the residue ignited as above described before making the color test with turmeric paper, the quantitative determination can be made by comparing with the color scale obtained from the aqueous solutions of boric acid as just mentioned. If the turmeric test is made by acidifying the urine with concentrated hydrochloric acid, dipping in the turmeric paper, and drying the latter, the quality of the red color is a little different, as above stated, so that accurate quantitative determinations cannot be made by comparison with the standards prepared from the aqueous boric acid solutions. In this case, however, the difficulty can be readily overcome by preparing the color standards by dissolving boric acid in normal urine and diluting with the latter instead of distilled water. The sample
of normal urine for this purpose may be obtained from the person experimented upon before the actual experiments are begun. An average sample from a number of normal individuals was also found to suffice for the purpose.

The bladder was emptied an hour before beginning the experiment and neither liquids nor food were taken during the time the feet were being soaked. The results are as follows:

Experiment 1.—The solution consisted of 6 liters of water plus 450 gm. of boric acid and 3 liters of 95 per cent alcohol. The feet were immersed at 2.27 p.m.

<table>
<thead>
<tr>
<th>Time</th>
<th>Urine Boric Acid Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.47 p.m.</td>
<td>0.001%</td>
</tr>
<tr>
<td>3.08</td>
<td>0.0015%</td>
</tr>
<tr>
<td>4.06</td>
<td>0.002%</td>
</tr>
<tr>
<td>5.05</td>
<td>0.005%</td>
</tr>
<tr>
<td>5.05</td>
<td>Discontinued soaking the feet.</td>
</tr>
<tr>
<td>5.30</td>
<td>The urine contained 0.01% per cent boric acid.</td>
</tr>
<tr>
<td>7.00</td>
<td>0.005%</td>
</tr>
<tr>
<td>10.00</td>
<td>0.002%</td>
</tr>
<tr>
<td>8.00 a.m.</td>
<td>0.002%</td>
</tr>
<tr>
<td>9.15</td>
<td>0.001%</td>
</tr>
<tr>
<td>11.30</td>
<td>0.001%</td>
</tr>
<tr>
<td>2.00 p.m.</td>
<td>traces of boric acid.</td>
</tr>
</tbody>
</table>

Experiment 2.—This was performed to see how soon after immersion of the feet in the boric acid solution that substance would appear in the urine. The experimental conditions were exactly as in Experiment 1. It was found that it required no longer than 5 minutes for the boric acid to make its appearance in the urine.

Experiment 3.—The solution consisted of 6 liters of water plus 1 gm. of each of the following: H₂BO₃, LiCl, RbCl, CsCl, and SrCl₂. The feet were immersed from 2.37 to 4.45 p.m. The bladder was then emptied and the urine tested as above described. Not a trace of any of the dissolved substances was found in the urine.

Experiment 4.—The foot bath consisted of a 5 per cent lithium chloride solution. The feet were then immersed for 30 minutes. No lithium was found in the urine.

Experiment 5.—The foot bath consisted of a 10 per cent lithium chloride solution. The feet were immersed for 42 minutes. No lithium was found in the urine. The entire experiment was repeated on the following day with the same result.

Experiment 6.—The foot bath consisted of a 10 per cent aqueous lithium chloride solution to which an equal volume of 95 per cent alcohol had been added. The feet were immersed for half an hour. Not even a spectroscopic trace of lithium was found in the urine.

Experiment 7.—The foot bath consisted of an aqueous solution of Li₃B₂O₇ which contained one-sixth of a mol per liter. The feet were soaked from
10.18 a.m. to 12.30 p.m. Seven samples of urine were taken at various intervals during this time, but not one of them contained even a trace of boric acid or lithium.

The experiment was repeated using Na₂B₄O₇ instead of Li₂B₄O₇. Again, not even a trace of boric acid was found in the urine.

Experiment 8.—This was like Experiment 7 except that lithium oleate was used instead of lithium borate. Not a trace of lithium was found in the urine.

Experiment 9.—This was like Experiment 7 except that lithium linolate was used instead of lithium borate. Not a trace of lithium was found in the urine.

Experiment 10.—This was like Experiment 7 except that lithium caseinate was used instead of lithium borate. Again, not a trace of lithium was found in the urine.

Experiment 11.—The foot bath consisted of 6 liters of a 10 per cent lithium chloride solution to which 200 cc. of 5 N hydrochloric acid had been added. The feet were immersed at 10.58 a.m. and samples of urine were taken after 5, 10, 20, 30, 40, and 60 minutes. Not even a spectroscopic trace of lithium was found to be present in any of these samples.

The urine before beginning the experiment was normal and faintly acid toward litmus. All five of the samples of urine tested after immersing the feet were slightly alkaline toward litmus; the last sample being decidedly more alkaline than the others.

In this solution the feet felt "hard" when rubbed against each other and not slippery as in the solutions in Experiments 7, 8, 9, and 10 which were, of course, alkaline.

Experiment 12.—The feet were immersed in 0.1 N H₂SO₄ solution for 10 minutes. After 5 minutes the urine was distinctly alkaline toward litmus and after 10 minutes the alkalinity was plainly more pronounced.

The normal faintly alkaline reaction of the saliva remained the same throughout the experiment.

Experiment 13.—The feet were immersed in 0.1 N citric acid for half an hour. Samples of urine were taken every 10 minutes during this time. The urine always remained normally faintly acid. This experiment was done from 3.30 to 4.30 p.m. of the same day as Experiment 11 which was carried on from 10.52 to 11.02 a.m. The feet soaked in 0.5 N citric acid solution actually increased the acidity of the urine. The saliva remained alkaline.

When 1 gm. of citric acid was taken internally by mouth, the urine was perceptibly more acid than normal, in 5 minutes. The same was found to be true when 5 cc. of 0.1 N H₂SO₄, diluted so as to be N/150, were taken internally.

Experiment 14.—The foot bath consisted of a 17.64 per cent aqueous solution of cane-sugar. The feet were immersed from 1.30 to 5.20 p.m. The sugar solution did not show any perceptible change in content and, of course, no sugar was found in the urine.
A review of the experiments performed shows that of all of the substances studied boric acid, and this alone, passes through the living skin in perceptible quantities. When salts of boric acid like borax or lithium borate are used, no boric radical is found in the urine. It requires free boric acid to pass through the living skin. Again, the amounts of boric acid found in the urine of a normal person whose feet are soaked in boric acid solution are much the same (only a few hundredths of a per cent) as those observed in patients treated with the boric acid compresses for blood poisoning. Why boric acid should possess this peculiar property of passing through the living skin which other substances, including salts of boric acid, are quite unable to penetrate, is hard to say. We are here evidently confronted with a highly specific property of boric acid. The solution of the latter probably is adsorbed by the skin (i.e. loosely combined with the latter) and from this loose combination the boric acid is swept away by the blood stream. It is remarkable that in 5 minutes after the feet are immersed in the boric acid solution, boric acid is present in the urine.

When persons suffering from blood poisoning are given boric acid by mouth, relatively large quantities of boric acid are found in the urine; but the infection is not quelled by this treatment. On the other hand, when the boric acid solution is put upon the skin, but very small amounts appear in the urine (though they get there rapidly), and the infection is conquered. Borates (like borax), when used topically in cases of blood poisoning, do not effect a cure, and we can now readily understand this, for these salts are quite unable to permeate the living skin.

All of the substances tested pass readily through dead human skin and also through other dead animal membranes. These substances also pass through the living mucous membranes of the mouth and alimentary canal. Now, since experiments on osmosis have demonstrated conclusively that the chemical nature of the membrane is the determining factor as to whether a substance will pass through the membrane or not, one is led to the conclusion that dead skin and living skin are chemically different, for they act quite differently osmotically. Similarly,
the living mucous membranes are chemically different from the living skin since they act differently osmotically. These latter two septa act alike when dead in that they let through all of the substances studied; but when living, the skin lets through boric acid only, while the mucous membranes are penetrated by all of the dissolved substances.

Whether small amounts of sodium or potassium salts may pass through the skin is hard to determine for salts of these metals are normally present in the body. For this reason, salts of other alkalies not normally present in the body were tested. Lithium seemed particularly suitable for this purpose since it is readily detected in minute quantities by means of the spectroscope. However, in none of the experiments (Nos. 3 to 11 inclusive) was even a trace of lithium found in the urine.

The alkalinity which developed in the urine when the feet were immersed in a hydrochloric acid solution (Experiment 11) or a sulfuric acid solution (Experiment 12) is very interesting. Evidently this stimulus causes reaction in the body to combat, i.e. neutralize these acids, which action is strong enough to continue to produce alkalinity. The weaker acid, citric acid (Experiment 13), does not have the same effect as hydrochloric or sulfuric acid. Stronger solutions of citric acid actually cause perceptibly greater acidity of the urine. This peculiar action still awaits adequate explanation. It is hoped to study the matter further, experimentally. However, it is clear that sulfuric, hydrochloric, and citric acids when taken by mouth acidify the urine, while when the skin is bathed with them the first two cause an alkaline reaction of the urine while the citric acid has the opposite effect. In the face of this, it does not seem so peculiar that boric acid also should have quite a different effect when taken internally from that produced when it passes into the system through the living skin.
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