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Original Articles

THE ELIMINATION OF CHLORIDS IN NEPHRITIS.

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Widal and Javal¹ recently called attention to the inability of many nephritics to eliminate sodium chlorid in a normal manner. The salt retained in the tissues required a certain amount of water to maintain it in the proper molecular concentration, thus leading to edema; they offer this as the probable cause of dropsy in nephritis. This chlorid retention was found chiefly in acute and chronic parenchymatous nephritis, and especially in patients who were edematous. This retention was not found in the interstitial form, and we know that when edema develops in these cases it is usually of cardiac origin. They, furthermore, decided that the impermeability of the kidney to urea and salts did not necessarily go hand in hand, as in the terminal period of Bright's disease there may be marked retention of chlorids, but none of urea, phosphates or sulphates. They report a case of uremia, with daily elimination of 28 grams of urea, but only 0.39 grams of sodium chlorid. For this reason they consider the chlorid elimination as a better index of the functioning power of the kidney than the excretion of urea, and that the unfavorable progress of a case is associated with reduced chlorid elimination. With the chlorid retention there is increased elimination of sulphates and phosphates, and as the chlorids increase these salts diminish.

Only small amounts of sodium chlorid are essential for the animal economy. According to Bunge, a person on a mixed diet requires daily 1 to 2 grams; most people, however, consume 10 to 20 grams. The excess of chlorid is eliminated chiefly through the kidneys. The normal feces contain less than a gram daily, but as a result of diarrhea this may be increased to 4 or 5 grams. The skin eliminates on an average 1,000 c.c. of sweat containing 1 to 2 grams of sodium chlorid. The total daily elimination may, of course, be greatly increased by sweating, and some recent results point to increased sodium chlorid in the perspiration of patients with chlorid retention. In diseases associated with polyuria, as diabetes insipidus or interstitial nephritis, the sodium chlorid intake and excretion may be greatly increased, often reaching 25 to 30 grams daily.

The view is generally held that when a large excess of sodium chlorid is administered to a healthy person this rapidly appears in the urine, the maximum excretion occurring three to four hours after ingestion. Since the

work of Widal, further study has been made² of the normal kidney and it has been found that the daily elimination of sodium chlorid suffers wide daily variation without any apparent cause. Koziczekowsky found on a fixed diet the daily elimination varied from 9.9 to 23.7 grams in one case and from 6.8 to 14.4 grams in another. He gave people with apparently healthy kidneys an additional 10 grams of sodium chlorid daily for three successive days, having previously estimated the daily output, and reports a chlorid retention of from 18 to 25 grams.

Patients with acute or chronic parenchymatous nephritis, when given, in addition to their usual diet, ten grams of salt, show only moderately increased chlorid in the urine. Except in very severe cases, the amount of urine is increased. When this increased ingestion of salt is continued for several days, the patients gain in weight due to the developing edema, the amount of albumin in the urine is increased, headache, nausea and stupor may develop; in short, a condition resembling uremia. Widal and Javal were able to make the edema appear and disappear at will by increasing or withdrawing the chlorids. The weight of one patient fluctuated from 56 to 60 kilos. The edema rapidly disappeared when the patient was placed either on a milk diet or on meat, bread and potatoes. The addition of ten grams of salt to either diet interfered with improvement. During the disappearance of the edema the daily amount of chlorids eliminated exceeded the intake 3.3 grams. The amount of albumin also decreased from 15 to 3.38 grams daily. When ten grams of salt was added to the milk daily, the urine decreased in amount and the daily retention of chlorids was 4.57 grams, the patient increasing 2.1 kilos in weight, the albumin increasing from 2.4 to 12.12 grams. The patient was then placed on a diet containing 400 grams of meat with bread and 2,500 c.c. of fluids. Within eleven days the weight decreased 3.7 kilos and the albumin had fallen to 0.72 grams daily, the edema reappearing when the salt was added to the diet. Numerous investigators have verified the above results. Koziczekowsky reports marked increase in the amount of chlorid in the various organs of patients with uremia. Courmont,³ in three cases of acute or subacute nephritis, injected subcutaneously normal salt solution. After the second day the urine became scant, and two of the patients developed

2. Only a few references are appended. A complete bibliography may be found in *Centralblatt f. innere Medizin*, 1903, No. 1. Most of the articles on the subject in foreign journals have been repeatedly summarized in the Foreign Current Literature Department of THE JOURNAL. Achard: "Retention des chlorures et pathogenie de l'edem," Soc. Méd. des Hôp. de Paris, July 31, 1903. "Hyperchloruration et déchloruration," *Ibid.*, Nov. 20, 1903. Achard and Loeper: "Rétention des chlorures dans les néphrites," Soc. Méd. des Hôp. de Paris, May, 1903. Chauffard: Soc. Méd. des Hôp., Paris, June 3, 1904. Illyes und Kövesi: Berlin. klin. Wochft., 1902; 1904, Nos. 24, 25 and 26. Strauss: *Zeitsft. für klin. Med.*, vol. xlvii.

3. Courmont: *Lyon Médical*, cl, 1903.

1. Widal and Javal: *Presse Médicale*, 41, 1903.

uremia. Nagelschmidt⁴ produced an artificial nephritis in dogs and demonstrated chlorid retention with increase of salt in the blood. Castaigne⁵ demonstrated that in animals with nephritis moderate amounts of sodium chlorid would double or triple the amount of albumin. He also reports that in patients with nephritis, without albuminuria, after the administration of salt, albumin appeared in the urine.

Kovesi has recently verified Widal's results and given some interesting additional information. Patients with chlorid retention increased in weight and became more edematous after ingestion of excessive amounts of salt, although the fluids taken during this time were not increased and the daily amount of urine not diminished. It must be that the elimination of water by other channels has been lessened. There was no increase in the liquids passed in the stool and there only remain the skin and lungs. He believes as a result of chlorid retention there is a lessening of the invisible perspiration. The amount of evaporation which takes place from the surface of the body is dependent not only on the moisture and temperature of the surrounding air, but also on the molecular concentration of the body fluids. The higher the osmotic pressure the less water is given up.

Soon after Widal's communication I began investigating the subject. The cases for study were obtained chiefly from the wards of Cook County and the Presbyterian hospitals. While no attempt was made to determine the exact intake of salt, the patients were kept on a fairly uniform diet during the period of investigation. In some cases this was milk only; in others, the light ward diet. The chlorids were estimated by the Volhard method. When possible, the patients were weighed daily. The sodium chlorid was administered at first in wafers, but, as this often produced nausea, it was later given in solution. The following method was pursued: The chlorids were estimated daily for nine consecutive days. The first three days the patient had merely the chlorids contained in his food; the following three days he received daily an additional ten grams; then the three following days merely the chlorids in his food.

In the accompanying table the total urine for each of the three-day periods is noted, the total chlorid in each period, the grams of chlorid retained at the end of the period when extra salt was given and the percentage of it in the urine during each period. During the second period ten grams of salt were administered daily, except in the cases indicated by an asterisk, where only five grams were given.

Two cases of acute nephritis were examined: one post-diphtheric with blood, epithelial and granular casts, but only a trace of albumin. There were marked uremic symptoms and moderate edema. The other was of six weeks' duration, the urine containing a large amount of albumin, many granular and epithelial casts, very slight edema. These patients were kept on an exclusive milk diet, consisting of 1,000 c.c. of milk and 250 c.c. of cream. One patient had a chlorid retention of 10.7, the other 24.8. In both there was a visible increase in the edema. One patient was weighed, gaining three pounds during the period, when extra chlorid was given, and losing it quickly after the salt was discontinued. In one case less urine was passed during the period of extra chlorid than in the preceding or following period.

The percentage of chlorid in the urine was increased following the administration of the salt.

Case.		Urine, three day periods, c.c.	Chlorids, gms.	Retained chlorids, gms.	Gms. chlorids per liter.
1. Acute nephritis, moderate edema.	1	1680	13.58		8
	2	2050	18.14	25.44	8.9
	3	2190	15.41		7.01
2. Acute nephritis, marked edema.	1	6950	31.8		4.6
	2	6300	36.14	*10.66	5.7
	3	7500	19.5		1.6
3. Chronic Parenchymatous nephritis; marked edema; myocarditis.	1	1150	1.		.86
	2	970	1.86	29.14	1.91
	3	2380	2.32		.97
4. Chronic parenchymatous nephritis; marked edema.	1	4050	20.		4.9
	2	4100	35.07	14.93	8.5
	3	3360	18.52		5.6
5. Chronic parenchymatous nephritis; marked edema.	1	5090	17.55		3.4
	2	5300	38.64	8.91	7.1
	3	7440	31.66		4.2
6. Chronic parenchymatous nephritis; slight edema.	1	3500	30.		8.5
	2	3800	40.	20.	10.5
	3	3725	29.25		7.8
7. Chronic parenchymatous nephritis; marked edema.	1	4600	28.06		6.1
	2	3800	24.96	33.1	6.5
	3	2950	20.51		7.0
8. Chronic parenchymatous nephritis, probable secondary contracted kidney; no edema.	1	4050	33.30		8.2
	2	5580	55.	*6.7†	9.8
	3	4270	21.75		5.1
9. Chronic parenchymatous nephritis; no edema.	1	6950	31.8		4.6
	2	6300	36.14	*10.66	5.7
	3	7500	19.5		2.6
10. Normal.	1	2340	37.41		7.
	2	5970	44.75	22.66	7.5
	3	5040	37.45		7.4
11. Normal.	1	6870	48.8		7.1
	2	9120	67.4	11.4	7.3
	3	7090	56.4		7.9
12. Normal.	1	7580	37.62		4.9
	2	7780	54.7	12.92	7.0
	3	5520	44.4		8.0
13. Normal.	1	3000	42.84		14.28
	2	4000	49.26	23.6	12.3
	3	3300	36.76		11.1
14. Myocarditis; general edema.	1	3906	24.		6.1
	2	9840	78.	24†	7.9
	3	2108	13.		6.1

* Patients received five grams extra chlorid daily.

† Eliminate in excess of chlorids ingested.

Seven patients with chronic parenchymatous nephritis were examined. Six had more or less edema. The patient without edema had probably a secondary contracted kidney. The six patients with edema all had a chlorid retention varying from 8.9 to 29.24 grams during the three days of extra salt. The secondary contracted kidney eliminated 6.7 grams more chlorid than was ingested. In two cases the urine decreased in amount during the period of extra chlorid. Two patients showed marked increase in the edema and both complained of increased headache and stupor. One patient was taking Basham's mixture. A later test was made, with patient taking two grams of diuretin daily, with much better chlorid elimination. The patient with the least chlorid retention died; the one with the greatest retention left the hospital much improved. In two cases with marked edema the albumin was estimated by the Purdy method and the effect observed of potassium acetate, potassium neutral phosphate and theocin on the chlorids and albumin. The results were practically identical in the two cases. During the period of extra chlorid the albumin was decidedly increased. None of the remedies used increased the elimination of chlorid.

Two patients with uremia were examined. Both of these died before the tests were completed, so do not appear in the table. In both cases the urine was scant

4. Nagelschmidt: Zeitf. für klin. Med., vol. 42.

5. Castaigne and Rathery: Arch. de Méd. expér. et d'anat. path., vol. xv, 1903.

and the daily amount of chlorids less than two grams. Following the administration of salt, the urine was lessened, one case from 500 to 240 c.c., and scarcely any of the extra chlorid appeared. The edema was decidedly increased and the patient's condition worse.

A patient with myocarditis, having fluid in the pleural, pericardial and abdominal cavities, showed marked increase in the daily urine following the administration of chlorids, and excreted 24 grams, or 8 grams daily more chlorid than was ingested. This patient showed actual improvement, which continued after the chlorid was discontinued. This might be considered an increased activity of the kidney due to the ingestion of large amounts of chlorid, analogous to the results of Claude, who found increased elimination of urea following the use of chlorids, or the results of Roque and Lemoine, who found increased activity of kidney to the phloridzin test after the use of common salt. In a single case of this sort, however, no conclusion should be drawn. While we are unable to disprove that excessive sodium chlorid stimulates kidney activity in certain cases, it appears doubtful, especially when we consider its action on the healthy kidney.

Four patients without apparent heart or kidney trouble were tested. All these showed a degree of chlorid retention almost, if not quite, equal to the nephritics. This difference might be mentioned in two, viz., the retained chlorid was eliminated within 48 hours after its discontinuance, while in nephritics it took place more gradually. In each case the administration of chlorids caused a marked increase in the amount of urine. Following the ingestion of the salt, the percentage of chlorids in the urine was increased, not, however, to such a degree as in the nephritics. No edema resulted. Assuming that the salt was absorbed from the intestinal tract, it must have remained in the tissues associated with sufficient water to maintain the proper dilution. In other words, these patients had an undemonstrable edema. The tissues of the nephritics were already water-logged so that any increase in edema was readily observed. In support of this view one of the patients was weighed daily and showed an increase in weight of $2\frac{1}{4}$ pounds following the administration of the chlorids. Novocourt and Vitry's experiments on nurslings is corroborative of this view. They administered daily for a period of seven days 0.25 to 1 gram of sodium chlorid, and found a greater increase in weight than for the same period on the same amount of food, but without the additional chlorid. They believe this is due to improved nutrition, but it is probably the result of water retention.

A summing up of the evidence would indicate that the chlorid retention in moderately severe nephritis is not greater than in the normal kidney. The terminal stages of nephritis, however, are characterized by very marked impermeability of the kidney to sodium chlorid. This difference, however, exists: in nephritics there is a visible increase in the edema, in the healthy individual there is no detectable edema. It is not necessarily true that a chlorid retention, after moderate excess of salt, exists in every healthy individual, but reports from various writers indicate that such is the rule.

Another phase of the question, and it would seem a much more important one, is the increase in the albuminuria and development of uremia symptoms following excessive chlorid ingestion. The view that the so-called uremia of nephritis is, in reality, a chloremia has little support. It appears that the increased cerebral

edema is the more probable explanation. From a therapeutic standpoint, whatever the final decision regarding the impermeability of the nephritic kidney to chlorid, there is no doubt that excessive salt should be avoided, as it causes not only water retention, but by increasing the osmotic pressure of the blood lessens perspiration and the amount of water lost by respiration. Two grams of sodium chlorid daily are sufficient for the animal economy. Milk contains from 1.2 to 1.7 grams per liter; 100 grams of bread, on an average 1.3 grams; 1,000 grams of beef, 1.15 grams. Widal reports disappearance of edema and general improvement on a diet consisting of meat, 400 grams; potatoes, 1,000 grams; sugar, 100 grams; butter (unsalted), 80 grams; fluids, 2,500 c.c. This diet contains only 1.5 grams of chlorid. Especially to be avoided are the soups and broths, as they contain large amounts of salt, the broths at the Cook County Hospital containing 11.3 grams per liter, and many patients drink 500 c.c. of this daily. The use of subcutaneous injections of salt is contraindicated, as it may favor the development of uremia. I do not believe that the degree of chlorid retention is necessarily an index of the extent of kidney incompetency. Two cases of nephritis with a mild degree of retention died, while the patient with the highest degree of retention left the hospital much improved.

CONCLUSIONS.

In patients with moderately severe nephritis associated with edema, the ingestion of large amounts of sodium chlorid is followed by a chlorid retention. The patient gains in weight, the edema becomes more marked, the albuminuria increases and symptoms may develop resembling uremia.

In patients with severe nephritis, and especially those with uremia, chlorid retention is very marked, as scarcely any of the extra chlorids administered are eliminated.

In individuals with apparently healthy kidneys, following the ingestion of sodium chlorid, there is a chlorid retention equal to that of mild nephritis. The individual gains in weight, but there is no visible edema, no albuminuria and no uremic symptoms appear.

THE PHARMACOLOGY OF DIETHYLOXY-ACETYL UREA.*

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Some weeks ago my attention was called to a new group of chemical bodies belonging to the methane series. According to A. H. C. Heitmann and Erik Clemmensen, the discoverers, they are condensation products of urea and the various oxyacetic acids. A consideration of the chemical structure of these compounds led to the belief that all would possess considerable hypnotic power, but the ethyl compound was thought to be the more promising for therapeutic purposes. The originators accordingly prepared and placed at my disposal sufficient quantities of the ethyl derivative in its pure state, and a little later its sodium salt, to undertake a series of animal experiments to demonstrate its pharmacologic properties.

Perhaps the most desirable chemical name that can be given to the compound, as indicating its structure, is the one mentioned in the title of the paper, diethyl-oxyacetyl urea. The chemical formula is given by

* Read before the central branch of the Am. Physiological Society, March 29, 1905, at Chicago.