STUDIES OF THE INORGANIC METABOLISM IN PNEUMONIA WITH ESPECIAL REFERENCE TO CALCIUM AND MAGNESIUM.*

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Most of the investigations which deal with the metabolism of inorganic substances in pneumonia have been devoted to the study of the chlorides. The retention of chlorine, perhaps the most easily demonstrable of the various disturbances of metabolism during fever, is so constant and so pronounced in pneumonia that it has assumed diagnostic importance. That much less attention has been paid to the excretion of the bases probably depends on the fact that somewhat more complicated analytical methods are needed.

The excretion of sodium and potassium was, however, comprehensively studied by Salkowski[1] who found that sodium, as well as chlorine, is retained during fever, but that potassium continues to be excreted. The normal relationship in which the amount of sodium excreted exceeds that of potassium, was shown to be reversed during the febrile stage of several cases of pneumonia. The metabolism of calcium was later investigated by von Moraczewski,[2] who demonstrated by balance experiments that there is a true retention of calcium in pneumonia which is as definite as is that of sodium or of chlorine. At the same time von Moraczewski made a few observations on the excretion of magnesium, in one case for a period of eight days, and in another for two days, and found no evidence of a retention. Beyond this, however, there is little mention in the literature of the metabolism of magnesium during pneumonia.

Tables I and II show the results of analyses for chlorine, calcium, and magnesium in the urine. They are typical examples of sixteen

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[1] Salkowski, E., *Virchows Arch. f. path. Anat.*, 1871, liii, 209.

[2] von Moraczewski, W., *Virchows Arch. f. path. Anat.*, 1899, clv, 11; *Ztschr. f. klin. Med.*, 1900, xxxix, 44.

TABLE I.

The Excretion of Chlorine, Calcium, and Magnesium in the Urine in Pneumonia.

No. of case.	Day of disease.	Temperature F.	Chlorine in gm.	Calcium oxide in gm.	Magnesium oxide in gm.
I	4	105.4	0.50	0.053	0.074
	5	102.4	0.88	0.023	0.383
	6	105.0	0.83	0.022	0.127
	7	99.4	0.73	0.040	0.260
	8	99.6	0.72	0.136	0.181
	9	98.8	1.45	0.161	0.101
	10	98.0	4.49	0.258	0.156
	11	98.2	5.93	0.408	0.225
	12	98.0	10.05	0.675	0.274
	13	97.6	9.33	0.686	0.243
II	9	99.4	3.95	0.017	0.455
	10	99.4	——	——	——
	11	98.8	4.49	0.053	0.467
	12	99.0	5.04	0.022	0.484
	13	97.8	7.71	0.340	0.364
	14	98.0	6.96	0.290	0.271
	15	98.0	3.34	0.174	0.165
	16	97.8	11.64	0.414	0.347
	17	98.6	5.98	0.312	0.282
IV	8	104.8	1.28	0.036	0.454
	9	104.0	1.18	0.023	0.240
	10	101.8	0.83	0.017	0.225
	11	101.2	1.00	0.032	0.133
	12	102.0	0.55	0.021	0.162
	13	100.8	0.99	——	——
	14	101.2	1.75	0.059	0.151
	15	102.0	3.81	0.109	0.141
	16	100.6	3.76	0.152	0.165
	17	100.4	4.73	0.201	0.139
	18	100.2	6.69	0.184	0.119
V	11	100.9	0.58	0.013	——
	12	100.5	0.75	0.039	0.307
	14	100.6	1.81	0.031	0.203
	18	99.0	5.74	0.076	——
VI	10	103.3	0.48	0.029	0.312
	13	101.7	1.00	0.019	0.123
	14	101.0	0.93	0.026	0.180
	18	99.8	6.43	0.099	0.146
IX	6	104.2		0.020	0.099
	7	99.0		0.017	0.215
	11	98.8		0.169	0.128
	12	98.4		0.223	0.205
	13	98.0		0.332	0.223
	14	98.0		0.344	0.194
X	5	104.5	0.13	0.008	0.008
	7	104.0	0.24	0.020	0.013
	8	103.4	0.37	0.041	0.051
	9	101.5	0.34	0.027	0.302

TABLE I.—*Continued.*

No. of case.	Day of disease.	Temperature F.	Chlorine in gm.	Calcium oxide in gm.	Magnesium oxide in gm.
X	11	99.0	1.13	0.017	0.313
	12	98.4	8.51	0.071	0.222
	13	98.0	14.03	0.084	0.181
	14	98.4	8.58	0.169	0.210
	15	98.0	15.94	0.208	0.226
	16	98.0	11.78	0.273	0.263
	17	98.0	13.38	0.273	0.251
XI	9	99.6	0.99	0.032	——
	10	99.4	3.85	0.043	0.169
	11	99.4	6.22	0.059	0.153
	12	98.4	7.43	0.104	0.215
	13	98.4	9.59	0.161	0.189
	14	98.4	8.08	0.132	0.213
	16	98.6	23.38	0.431	0.221
XII	3	104.4	0.62	0.018	0.214
	4	104.2	1.56	0.020	0.367
	5	104.2	3.28	0.022	0.209
	6	104.0	4.29	0.021	0.341
	7	103.0	3.08	0.050	0.281
	8	98.6	2.92	0.098	0.236
	9	98.2	7.29	0.136	0.042
	10	98.4	15.86	0.351	0.082
	11	98.8	17.71	0.321	0.250
	12	99.4	12.48	0.206	0.192

Case XII received 10 gm. of sodium chloride daily. Case VII received 2 gm., cases VIII and XIV, 4 gm., and cases XIII and XV, 6 gm. of calcium lactate daily in addition to their diet. (For cases XIV and XV, see table II.)

cases of pneumonia in which rather extensive studies of the urine were made. They show, in agreement with von Moraczewski, that there is constantly a retention of calcium during the height of the disease. This calcium retention persists often for some days after the temperature has fallen to normal, and the excretion of calcium begins almost simultaneously with the excretion of chlorine. The figures for magnesium are also remarkably uniform and indicate clearly that this base is not retained, but that it is excreted normally in both febrile and afebrile stages of the disease. In many instances, indeed, in spite of the restricted diet, there is definitely more magnesium excreted during the fever than there is after the fever has passed. The only case in which there was any evidence of a retention of magnesium was seen in case X. In this case, however, on the three days on which low quantities of magnesium were

TABLE II.

No. of case.	Day of disease.	Temperature F.	Chlorine in urine in gm.	Calcium oxide in urine in gm.	Magnesium oxide in urine in gm.	Calcium oxide in feces in gm.	Magnesium oxide in feces in gm.	Approximate calcium oxide intake in gm.	Approximate magnesium oxide intake in gm.
XIV	4	104.8	0.56	0.024	0.100	—	—	—	—
	5	104.3	0.61	0.028	0.183	—	—	—	—
	6	104.0	0.41	0.011	0.213	—	—	—	0.22
	7	104.6	0.27	0.014	0.151	2.790	0.334	3.0	0.21
	8	100.4	0.13	0.029	0.264	4.091	0.493	3.0	0.20
	9	100.6	—	—	—	—	—	—	—
	10	100.6	2.82	0.050	0.313	2.642	0.355	2.6	—
	11	100.0	3.49	0.140	0.256	1.015	0.358	3.0	—
	12	100.0	3.61	0.162	0.202	2.681	0.418	3.2	—
	13	99.6	7.62	0.305	0.233	3.517	0.582	3.2	—
	14	99.0	9.02	0.267	0.175	2.548	0.378	3.2	—
	15	99.6	11.30	0.315	0.194	1.223	0.213	3.4	—
	16	98.6	10.27	0.374	0.249	1.413	0.261	3.0	—
	17	98.6	—	—	—	2.064	0.330	—	—
XV	5	105.5	}	0.1793	0.538	—	—	3.5	0.20
	6	105.4	}			1.269	0.645	4.7	0.32
	7	105.9		0.162	0.152	1.272	0.234	5.9	0.44
	8	105.8		0.109	0.155	3.475	0.433	4.3	0.28
	9	105.7		0.084	—	2.273	0.480	4.1	0.27
	10	104.6		0.062	—	1.765	0.213	4.5	0.30
	11	104.2		—	—	2.258	0.261	—	—

excreted, the urine contained amounts of albumen which were much larger than are ordinarily found in pneumonia. It is probable, then, that the retention of magnesium depended here upon a nephritis, which Rumpf[3] has shown may interfere with the excretion of any of the inorganic bases. This view is borne out by the fact that the sudden rise in the magnesium excretion coincided with a marked drop of the albumen in the urine. The demonstration that the excretion of magnesium goes on normally in pneumonia during the period in which calcium and chlorine are retained, is a point of evidence against the frequently recurring suggestion that chloride retention depends on a kidney lesion.

In order to be certain that a calcium starvation was not giving rise to a urinary picture which might simulate a retention of calcium, several patients received calcium lactate (four to six grams daily) in addition to the calcium in their regular diet. As the diet, especially in the febrile period, contained considerable amounts of milk, the daily calcium intake was a liberal one. That there is no

[3] Rumpf, Th., *München. med. Wchnschr.*, 1905, lii, 393.

especial difference in the absorption of calcium from the intestine in the febrile and afebrile periods is shown by cases XIV and XV, in which the stools were analyzed for calcium and magnesium. The food was not analyzed, but inasmuch as during the febrile period the patients were practically on a milk diet and as all food was measured with great care, it is possible to calculate fairly closely the intake of calcium and magnesium. Unfortunately in both these cases specimens of urine were lost, so that the results for certain days had to be thrown out, but in spite of this they both show that the excretion of magnesium in the urine and feces greatly exceeded the intake. There is thus a loss of magnesium to the body during the febrile period. The relation between the amount of magnesium in the feces and that in the urine was about the same in the two periods.

The disturbance of the urinary excretion of inorganic substances in pneumonia is, therefore, profound. On the one hand, there is a retention in the body of sodium, calcium, and chlorine. On the other hand, there is a normal or excessive excretion of potassium and magnesium. The normal quantitative relation of sodium to potassium and of calcium to magnesium is reversed in the febrile urine. It is interesting that sodium and calcium, the retained bases, occur in larger proportions than do magnesium and potassium in body fluids. In muscle the ratio is reversed. The excessive excretion of potassium and magnesium during fever thus falls in line with the high nitrogen excretion, and all three undoubtedly represent the increased tissue catabolism. This general type of metabolism is undoubtedly characteristic of fever or infection. It is not to be supposed that it is in any way specific for pneumonia, but the sharp change from the febrile to the afebrile period in lobar pneumonia gives an unusually good opportunity for studying the process.

ANALYSES OF THE BLOOD DURING AND AFTER THE FEBRILE PERIOD.

In order to study the mechanism of the retention of inorganic substances more directly, the blood was analyzed during the period of retention and again after excretion had begun. The quantitative estimation of chlorine in the blood is comparatively simple and, as the amount of chlorine present is considerable, the errors are small

and the results more reliable than in the case of calcium. A number of isolated observations have already been made on the chlorine content of the blood in pneumonia. Thus Biernacki,[4] Jarisch,[5] Runeberg,[6] Laudenheimer,[7] and Schenk[8] have each reported one or two cases in which they found a decrease in the chlorine content during fever, and in Schenk's case there was a rise during convalescence. Vanderhoof[9] gives two cases with figures for the febrile period which are slightly below his average. One of these showed a fall on the day after the crisis. von Moraczewski[10] has made a more thorough study and has reported eight cases, most of which showed a diminution of chlorine in the blood during the fever. In three cases a second examination was made after the crisis and in two a rise was noted, while in one there was a fall in chlorine. Santini[11] states that the chlorine content of the blood is higher during the febrile period than afterward. Hutchison[12] analyzed pleuritic effusions from cases of pneumonia and found that they contained less chlorine than effusions in other diseases.

To obtain as complete information as possible about the chlorine content of the blood during fever and about the relation of changes in the blood to changes in the urinary excretion, eight cases were studied and twenty-three observations were made (table III). The blood was taken during the period of chlorine retention, and in five cases again shortly after chlorine excretion had begun. Several of the cases were given sodium chloride by mouth to avoid having a chlorine starvation. Eight control observations on one normal adult and four syphilitics (without fever) gave an average normal chlorine content of 0.276 of a gram per 100 grams of blood. In only one case of uncomplicated pneumonia was this figure approached during the first period. The other cases show a much

[4] Biernacki, E., *Ztschr. f. klin. Med.*, 1894, xxiv, 460.

[5] Jarisch, A., abstracted in *Jahresb. ü. d. Leistung. in d. ges. Med.*, 1877, i, 165.

[6] Runeberg, J. W., *Deutsch. Arch. f. klin. Med.*, 1884, xxxv, 266.

[7] Laudenheimer, R., *Ztschr. f. klin. Med.*, 1892, xxi, 513.

[8] Schenk, S. L., abstracted in *Jahresb. ü. d. Leistung. in d. ges. Med.*, 1873, vii, 129.

[9] Vanderhoof, D., *Jour. Am. Med. Assn.*, 1908, li, 478.

[10] von Moraczewski, W., *Virchows Arch. f. path. Anat.*, 1896, cxlvi, 424.

[11] Santini, A., *Riforma med.*, 1903, xix, 477.

[12] Hutchison, R., *Jour. Path. and Bacteriol.*, 1898, v, 406.

lower chlorine content of the blood during chlorine retention, and all cases examined show a rise of the chlorine in the blood when the chlorine begins to be excreted in the urine. The third observa-

TABLE III.

No. of case.	Date.	Temperature F.	Chlorine per 100 gm. of blood.		Chlorine excreted in urine for 24 hours.	Remarks.
			During chloride retention	During chloride excretion.		
I	Mar. 19	104.4	0.226	——	——	Three hours before death.
II	Mar. 20	104.0	0.266	——	0.00	
	Mar. 21	103.3	0.265	——	0.35	
	Mar. 22	102.2	0.276	——	0.48	
	Mar. 25	99.0	0.276	——	1.00	Blood taken 1½ hours after eating 10 gm. of sodium chloride.
	Mar. 31	99.5	——	0.285	4.39	
III	Mar. 21	99.5	0.253	——	0.53	Crisis during preceding night.
	Mar. 22	99.0	0.252	——	0.58	
	Mar. 24	98.0	——	0.291	4.70	
IV	Mar. 23	101.9	0.254	——	0.00	
	Mar. 24	99.2	0.254	——	1.06	
	Apr. 3	Normal	——	0.293	5.74	
	Apr. 4	Normal	——	0.285	——	
	Apr. 13	Normal	——	0.273	——	
V	Apr. 5	101.6	0.256	——	0.10	Received 5 gm. of sodium chloride twice daily, beginning April 5.
	Apr. 6	102.0	0.245	——	0.08	
	Apr. 15	99.6	0.274	——	0.70	Developed acute nephritis.
VI	Apr. 18	102.0	0.224	——	0.00	Received 5 gm. of sodium chloride twice daily, beginning April 18.
	Apr. 20	99.8	——	0.277	4.27	
	Apr. 22	98.4	——	0.261	3.61	
VII	Apr. 25	102.5	0.256	——	0.38	
	May 1	Normal	——	0.276	2.11	
VIII	Mar. 28	103.0	0.245	——	——	Received 5 gm. of sodium chloride on the evening before, and 5 gm. of sodium chloride three hours before blood was taken.

tion in case V shows a rise of chlorine in the blood without a corresponding rise in the urine, but at this time a severe acute nephritis had set in, so that the blood finding is characteristic for that condition. The results obtained thus agree with the bulk of previous

evidence, and make it certain that chlorine retention in pneumonia is associated with a low chlorine content of the blood.

There is very little available evidence as to the calcium and magnesium content of the blood in pneumonia. Both of these bases are present in such small quantities that a large amount of blood must be taken for analysis, and even then the error is liable to be considerable. von Moraczewski[13] gives the results of analyses for calcium of two specimens of blood from persons who had died of pneumonia. These contained 0.003 and 0.002 of a gram of calcium per 100 grams blood. In another paper[14] he reports several analyses for calcium, but they were made in specimens of only seven to fifteen cubic centimeters of blood, and the precipitates were so small that he puts no value on the results. Jarisch[15] found a higher percentage of calcium in the blood of a patient with pneumonia than in a specimen of normal blood. Nicholls,[16] using the method of Bell and Hick,[17] reports finding a low calcium index in pneumonia.

Table IV shows the results for calcium and magnesium obtained in the analysis of blood from seven patients during and after the period of calcium retention. Each determination was made in a specimen of 100 to 125 cubic centimeters of blood, but the figures for both bases are so small that the results are much less satisfactory than was the case with chlorine. In the two cases, however, in which blood was taken both during and after the period of calcium retention, the amount of calcium in the blood was lower during retention than it was after excretion had begun. The seven individual analyses during the period of retention show considerable variations, but the average is lower than the average of the four observations made in the normal period. It is certain, then, that there is no accumulation of calcium in the blood, as often occurs in nephritis.[18] The results suggest that in pneumonia the mechanism of calcium retention is the same as that of chlorine, and that their retention bears no relation to kidney lesions. Since it is generally

[13] von Moraczewski, W., *Ztschr. f. physiol. Chem.*, 1897, xxiii, 483.
[14] von Moraczewski, W., *Virchows Arch. f. path. Anat.*, 1896, cxlvi, 424.
[15] Jarisch, A., *loc. cit.*
[16] Nicholls, *Proc. and Tr. Royal Soc. Canada,* 1910, ser. 3, iv, sec. iv, 85.
[17] Bell, W. B., and Hick, P., *Brit. Med. Jour.*, 1909, i, 592.
[18] Dennstedt, M., and Rumpf, Th., *Ztschr. f. klin. Med.*, 1906, lviii, 84.

TABLE IV.

The Calcium and Magnesium Content of the Blood in Pneumonia.

No. of case.	Date.	Temperature F.	Calcium oxide in 100 gm. of blood.		Calcium oxide excreted in urine for 24 hours.	Magnesium oxide in 100 gm. of blood.		Magnesium oxide excreted in urine for 24 hours.	Remarks.
			During calcium retention.	After calcium excretion had begun.		During calcium retention.	After calcium excretion had begun.		
I	Mar. 18	Normal	——	0.0072	——	——	0.0068	——	Temperature normal for 17 days.
II	Mar. 16	104.5	0.0065	——	0.024	0.0064	——	0.100	Received 4 gm. of calcium lactate daily.
	Mar. 19	104.0	0.0064	——	0.011	0.0058	——	0.151	
	Mar. 26	Normal	——	0.0092	0.267	——	0.0078	0.175	
	Mar. 28	Normal	——	0.0068	0.374	——	0.0076	0.249	
III	Mar. 17	104.0	0.0077	——	0.020	0.0074	——	0.099	Received 2 gm. of calcium lactate daily.
	Mar. 23	Normal	——	0.0092	0.223	——	0.0094	0.205	
IV	Mar. 28	103.0	0.0074	——	0.013	0.0059	——	0.191	Received 4 gm. of calcium lactate daily.
V	Apr. 9	105.3	0.0078	——	0.010	0.0057	——	0.075	Received 6 gm. of calcium lactate daily.
VI	Apr. 11	102.0	0.0080	——	0.053	——	——	0.142	Received 4 gm. of calcium lactate daily.
VII	Apr. 7	105.5	0.0073	——	——	0.0072	——	——	Urines for April 6 and 7 mixed. The 48 hour specimen contains 0.179 gm. of calcium oxide and 0.538 gm. of magnesium oxide. Received 6 gm. of calcium lactate daily.

conceded that the sodium that is retained is combined with chlorine, it is safe to conclude that the excretion of calcium, sodium, and chlorine is hindered by the same cause.

In the blood the amount of magnesium, like that of calcium, varies somewhat from case to case, but in the two instances in which the blood was examined during the febrile, and later during the afebrile period, the quantity of magnesium was found to rise after the fall of fever. Similarly, the average of all the examinations made during the febrile period is slightly, but distinctly lower than those made in the afebrile period. The condition is thus exactly similar to that found in the analyses for calcium, and this is more interesting since, under the circumstances, magnesium is excreted in large amounts, while calcium is scarcely excreted at all. In his case of pneumonia Jarisch[19] also found no increase in the magnesium over that in his control. Thus the evidence as to the amount of calcium and magnesium in the blood and their excretion by the kidney during fever shows that the essential factor in explaining excretion and retention is neither the kidney nor the blood, but that in order to find an explanation one must go back a step farther to the tissues themselves. In the case of magnesium the tissues continually give up a large amount of the base to the blood and this is readily and normally excreted by the kidney, so that there is no accumulation in the blood. Calcium, on the other hand, is retained in them and given off to the blood only in small amounts. To explain the fact that the magnesium content of the blood is lower during fever than afterwards is difficult, but one may perhaps suggest that at a time when sodium and calcium are being excreted in very small amounts, the kidney is able to excrete magnesium and potassium even more easily than normally.

THE RETENTION OF SALTS IN THE TISSUES.

It would seem *a priori* comparatively easy to demonstrate the presence of these retained substances in the tissues. Many investigations have been made to discover in what tissues retention takes place, but although differences may be found between the chlorine content of organs from patients with pneumonia and from patients

[19] Jarisch, A., *loc. cit.*

dying of other diseases, these are usually not marked enough to prove that any one organ acts as a storehouse. While more chlorine is found in the pneumonic lung than in the normal lung, the difference by no means accounts for the degree of retention in many cases. As examples of the amount of chlorine that may be retained in the pneumonic exudate, two cases may be cited in which one lung was practically completely solidified and the other quite free of signs of pneumonia. In the first case the normal lung contained 1.022 grams of chlorine, and the pneumonic lung 2.838 grams. The second patient had received ten grams of sodium chloride in the two days before death and had excreted practically none. The normal lung contained 0.715 of a gram of chlorine, and the solidified lung 2.916 grams. Thus in neither case was much more than two grams of the retained chlorine accounted for in the lungs. The majority of observers have found even less retention in the other organs. The small amount of chlorine found in the tissues is the more surprising when one realizes the extent to which retention may be carried. One patient received ten grams of sodium chloride daily for six days, and during the same period excreted less than sixteen grams.

On account of the work of Padtberg,[20] who showed by intravenous injections of sodium chloride in dogs that the skin is a storehouse for chlorine, it seemed worth while to determine the chlorine content of the skin in pneumonia, especially as there are very few analyses of skin on record. The skin of two control cases contained 0.196 per cent. and 0.178 per cent. of chlorine respectively. Skin from three patients who died of pneumonia contained respectively 0.169 per cent., 0.193 per cent., and 0.194 per cent. of chlorine. The difference between the controls and the pneumonia cases is thus too small to be of any importance. Santini[21] also found no evidence of any especial retention in the skin.

The evidence at present points to the fact that the retained salts are deposited in the tissues throughout the body, and that the percentage increase in any one organ is so slight that it is not brought out strikingly by the chemical analysis.

[20] Padtberg, J. H., *Arch. f. exper. Path. u. Pharmakol.*, 1910, lxiii, 60.
[21] Santini, A., *loc. cit.*

METHODS.

The chlorine in the urine was titrated according to the method of Harvey[22]. Calcium and magnesium in the urine were determined by McCrudden's[23] method.

In the analyses for chlorine in the blood, about 15 to 20 c.c. of blood were taken into oxalate solution. The coagulable proteid was precipitated by adding 20 per cent. magnesium sulphate and 1 per cent. acetic acid, boiling, neutralizing with 1 per cent. sodium hydrate, and boiling again. The chlorine was titrated in the filtrate. Calcium and magnesium were determined in samples of 100 to 130 c.c. of blood. The blood was ashed in a platinum crucible, according to Bunge's[24] method, and the bases were determined by McCrudden's method. Tissues were ashed similarly, and the chlorine was titrated.

I am greatly indebted to Miss Vinograd for much assistance in the analytical work.

CONCLUSIONS.

During pneumonia the metabolism of inorganic substances deviates markedly from the normal. While chlorine, sodium, and calcium are retained in the body, potassium and magnesium are excreted normally or in excess. Two cases showed a definite loss of magnesium to the body in the febrile period.

During the period of retention the chlorine content of the blood is distinctly lower than normally, the calcium content is apparently slightly lower, and the magnesium content tends also to be a little lower.

The skin is shown to play no special part in the chlorine retention. Since no organ or organs have been shown to store up large amounts of the retained substances, it is probable that they are spread diffusely throughout the body.

[22] Harvey, S. C., *Arch. Int. Med.*, 1910, vi, 12.
[23] McCrudden, F. H., *Jour. Biol. Chem.*, 1911–12, x, 187.
[24] Bunge, G., *Ztschr. f. Biol.*, 1876, xii, 191.