ON THE RELATIVE PROPORTIONS OF SODIUM, POTASSIUM, CALCIUM, AND MAGNESIUM IN BLOOD PLASMA IN RENAL DISEASE.*

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Since the introduction of microchemical methods for the estimation of sodium, potassium, calcium, and magnesium in blood (1915), a fair volume of literature has accumulated with particular reference to the part that alterations in the concentration of these elements may play in disease. Practically no consideration has, however, been given to the possible influence of another form of disturbance; namely, the alteration, not only in concentration, but in the relative proportions of the individual constituents.

Before the extensive studies of Macallum (1903) very few analyses of the inorganic composition of body fluids were made and the biological importance of such a study was not fully appreciated. In the invertebrate kingdom, only the Crustacea, Mollusca (Griffiths, 1892), and Limulus polyphemus (Genth, 1852; Gotch and Laws, 1885) were studied. Mammalian plasma, including that of the ox, pig, horse, and dog, was analyzed by Bunge (1876) and that of the sheep, goat, rabbit, cat, horse, ox, pig, and dog by Abderhalden (1897). Schmidt (1850) first recorded the analyses of human serum.

From the result of a study of the inorganic composition of the Medusa, Aurelia and Cyanea, Macallum (1903) concluded that in many invertebrates with a vascular system still freely communicating with the exterior, the circulating fluid is sea water. The same author then advanced the view that the blood plasma

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of vertebrates and invertebrates with a closed circulatory system is, in its inorganic salts, but a reproduction of the sea water of the remote geological period, in which the prototypic representatives of such animal forms first made their appearance. Thus in comparing the values he found for blood serum with those of ocean water previously determined (Dittmar, 1873–76) the following results were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Ca</th>
<th>Mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood serum</td>
<td>100</td>
<td>6.69</td>
<td>2.58</td>
<td>0.8</td>
</tr>
<tr>
<td>Ocean water</td>
<td>100</td>
<td>3.66</td>
<td>3.84</td>
<td>11.99</td>
</tr>
</tbody>
</table>

In a subsequent communication Macallum (1904) amplified these observations and explained the discrepancy in the magnesium values. In 1910 the same author made a series of analyses on vertebrates and invertebrates with a closed system, including the Gadus callarias (cod), Pollachius virens (pollock), Limulus polyphemus (horseshoe crab), Homarus americanus (lobster), Acanthias vulgaris (dogfish), and the whale. In this investigation he found a uniformity of the composition of the internal medium and concluded that this uniformity was a powerful factor influencing the course of evolution. "The capacity of the organism to make and keep its own internal medium uniform gives an enormous advantage to it, for it can change its habitat and adapt itself to a new environment without affecting the stable conditions under which its own tissues and organs do their best work. The organ which enables the organism to maintain these paleoceanic conditions is the kidney and this was its first function. The firmly fixed physiological habit or function must be the more ancient one, and consequently the earliest function was not the elimination of waste metabolic products, but the regulation of the inorganic composition of the blood."

The possible application of these observations to clinical medicine appears to have been overlooked, since no study of the blood plasma from this point of view, in conditions in which the function of the kidney is regarded as impaired, was made until the same author (1917) recorded his results in four cases of eclampsia. These showed that at least temporarily in eclampsia
### Table I.

<table>
<thead>
<tr>
<th>No.</th>
<th>Na (mEq.)</th>
<th>K (mEq.)</th>
<th>Ca (mg%)</th>
<th>Mg (mg%)</th>
<th>Clinical diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3827</td>
<td>45.18</td>
<td>6.91</td>
<td>2.16</td>
<td>0.64</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>4325</td>
<td>71.95</td>
<td>1.36</td>
<td>2.75</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>927</td>
<td>20.75</td>
<td>7.89</td>
<td>1.80</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>4525</td>
<td>31.86</td>
<td>2.95</td>
<td>0.84</td>
<td>0.85</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>3805</td>
<td>20.50</td>
<td>1.00</td>
<td>0.64</td>
<td>0.64</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>5644</td>
<td>23.90</td>
<td>1.10</td>
<td>0.85</td>
<td>0.85</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>1071</td>
<td>20.75</td>
<td>7.89</td>
<td>1.80</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>2549</td>
<td>20.50</td>
<td>1.00</td>
<td>0.64</td>
<td>0.64</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>3441</td>
<td>20.75</td>
<td>7.89</td>
<td>1.80</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>90-24</td>
<td>20.75</td>
<td>7.89</td>
<td>1.80</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>1360-24</td>
<td>20.75</td>
<td>7.89</td>
<td>1.80</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>6273</td>
<td>20.50</td>
<td>1.00</td>
<td>0.64</td>
<td>0.64</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>4288</td>
<td>20.75</td>
<td>7.89</td>
<td>1.80</td>
<td>0.91</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
<tr>
<td>6445</td>
<td>20.50</td>
<td>1.00</td>
<td>0.64</td>
<td>0.64</td>
<td>Chronic nephritis; uremia; myocarditis.</td>
</tr>
</tbody>
</table>

**Notes:**
- *Diabetic coma. Chronic nephritis.*
- *Eclampsia.*
- **Polycythemia vera.**
the kidneys concerned in maintaining the normal ratio of potassium in the blood plasma suffer a partial or total suppression of function. In the course of a study of renal function observations were made by the writer from the above point of view. The results are of sufficient interest to justify their publication.

**Material.**

The data were obtained from the analyses of twenty-three patients suffering from advanced renal or cardiac disease. An opportunity was afforded to make observations on two cases of polycythemia vera and these are also tabulated. The combined data are recorded in Table I. Under the heading of clinical diagnosis only the predominant clinical features are recorded. The data are recorded, not in order of the time of admission of the patients to the hospital, but in order of the degree of impairment of renal efficiency, as indicated by the concentration of non-protein nitrogenous elements (urea and creatinine) in the blood.

**Methods.**

In the experience of the writer, the microchemical methods for the estimation of Na, K, Ca, and Mg were found unsatisfactory. That he is not alone in this experience is evident from the literature. Since Hamburger (1915) first attempted to employ small quantities of fluid for such determinations, no less than twenty-one different modifications are recorded for the various elements. The methods followed in this investigation were those employed by Macallum in his original communications with slight modification, and they are as follows:

*Estimation of Sodium and Potassium.*

The fluid (30 to 40 gm.) is weighed in a platinum crucible or capsule, evaporated on a water bath to dryness, and the evaporation completed in an oven at a temperature of about 110°C. for 7 to 8 hours. After cooling in a desiccator, the preparation is weighed and the percentage of solids in the fluid determined.

The crucible or capsule is now heated over a Bunsen flame to a temperature that causes the fumes to arise from the residue. These latter should catch fire and burn above the residue. The heat is continued at this low temperature until all the volatile matter is gone. Then the residue is
kept at a dull red heat for varying periods according to the mass of the residue in order to carbonize it completely.

The carbonized residue is now extracted repeatedly with hot water and the extracted fluids are all combined. The residue is now dried and made to undergo complete combustion, and the ash set free is treated with dilute hydrochloric acid, the resulting fluid filtered, and the filtrate added to the combined extraction fluids.

The latter should be evaporated, on a water bath, to about 50 cc. To it is then added a saturated solution of baryta which precipitates all the phosphoric and sulfuric acids as phosphate and sulfate of barium. These are filtered off and the filtrate, received into the platinum capsule, is evaporated down to dryness and the residue fused completely with water-free oxalic acid.

The fused residue is now dissolved in the smallest possible quantity of water (2 to 3 cc.), filtered through the smallest possible filter into a platinum capsule, and the filtrate evaporated down to dryness, carefully heated over a Bunsen flame, and dissolved once more in 2 to 3 cc. of water. If the resulting solution is not clear, it must be filtered again. When clear, a small quantity of hydrochloric acid is added to it, and it is evaporated to dryness. The residue consists now wholly of the chlorides of sodium and potassium, which after being heated in the capsule to dull redness and then cooled may now be weighed.

To determine how much potassium and sodium there is in the mixture one adds an approximately calculated quantity of 10 per cent platinum chloride solution to the solution of the two salts, and the mixture is evaporated down, with frequent stirring, to dryness on a water bath. If sufficient platinum chloride is added then all the potassium chloride is in combination with it. The remainder of the platinum chloride enters into combination with the sodium chloride.

On the dried double salts one places 20 to 30 cc. of absolute alcohol and allows the preparation to stand under cover for an hour. Then to this is added 10 to 15 cc. of ether, and the mixture is then allowed to stand for a further hour.

The mixture of ether and alcohol is then carefully decanted from the residue and a fresh quantity of alcohol and ether (20 to 30 cc. of alcohol and 10 to 15 cc. of ether) is added and allowed to stand for another hour, then decanted, and a fresh quantity is poured on for another hour. The residue is then thoroughly dried at room temperature and the platinum in it reduced to the metallic condition by heating in hydrogen to 250°C.

The residue is then treated with water, the platinum filtered off, the filter containing it burned, and the metallic platinum weighed. From this weight can be calculated the quantity of potassium present, also the quantity of potassium chloride, and by subtracting the thus calculated amount of the latter from the combined weights of the two chlorides, the quantity of the sodium chloride may be ascertained.
Estimation of Calcium and Magnesium.

To the weighed quantity of plasma (25 to 30 gm.), placed in a platinum dish, about 2 gm. of pure sodium carbonate are added; the moisture, after being carefully stirred, is evaporated to dryness, the residue carbonized, then extracted several times with hot water, acidulated with hydrochloric acid, the remainder of the residue completely incinerated, the ash extracted with hot dilute hydrochloric acid, the fluid filtered, and the filtrate added to the volume of the united filtrates previously obtained.

The united filtrates are then treated with crystals of ammonium oxalate and ammonia, and after standing 24 hours the calcium oxalate precipitate is removed, incinerated to a constant weight, and weighed as CaO. From the filtrate the magnesium is precipitated as magnesium phosphate by the addition of ammonium phosphate and ammonia.

DISCUSSION.

The average normal ratios as recorded by Macallum are as follows: Na, 100; K, 6.11; Ca, 2.71; and Mg, 0.85. It will be noted that in only five of the twenty-three cases of cardiorenal disease could it be definitely stated that there was a disturbance in ratios of any of the elements. Both from the clinical diagnosis and blood urea nitrogen data it is obvious that in more than half of these cases (fourteen) there was a marked impairment of renal efficiency. All these patients died. With the exception of the one case of eclampsia in which a disturbed ratio was found, the remainder of disturbed ratios are all found in the advanced (uremic) cases. That there were nine other such cases which showed normal ratios in spite of the advanced renal lesions appears to emphasize further the fundamental nature and primary importance of this function of the kidney. An observation which may by further studies be found significant is that in each of the five cases with the high potassium ratios, the heart at autopsy (Dr. L. J. Rhea) was found markedly dilated. The electrocardiographic tracings (Dr. C. C. Birchard) in these cases were normal, in as far as the spread of excitation wave over the ventricles, duration of refractory period, and conduction interval of the bundle of His were concerned.

I wish to express my sincere thanks to Prof. A. B. Macallum for his kind interest, and also to Miss Althea Frith for assistance in this work.
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