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IS THE ANTAGONISTIC ACTION OF SALTS DUE TO OPPOSITELY CHARGED IONS?

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I.

The writer has shown in earlier papers[1] that a pure solution of NaCl of that concentration in which this salt occurs in sea water kills the newly fertilized eggs of the marine fish *Fundulus* so rapidly that they are unable to form an embryo, and that the addition of a small amount of certain salts with a bivalent metal (*e.g.*, Mg, Ca, Sr, Ba, Pb, Zn, Mn, Co, etc.) prevents this injurious action of NaCl. That this result could not be explained on the assumption that the egg needs Mg or Ca or Zn for its development was proven by the fact that in twice distilled water the same eggs not only can develop perfectly normally, but that the young fish can hatch and live. The only inference was that the pure NaCl solution in that concentration in which it is contained in the sea water injures the egg, while the addition of $CaCl_2$ (or the other salts with a bivalent cation) prevents this injurious action.

In order to explain the latter result and the antagonistic effect of $CaCl_2$, the writer suggested in 1905[2] that the NaCl, in a sufficiently high concentration, rendered the membrane of the egg which was normally impermeable to NaCl (and other salts) permeable for salts, and that the addition of $CaCl_2$ prevented this injurious effect of NaCl and preserved the normal imperme-

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[1] *Amer. Journ. of Physiol.*, iii, p. 327, 1900; vi, p. 411, 1902; *Arch. f. d. ges. Physiol.*, lxxxviii, p. 68, 1901; Loeb and Gies: *ibid.*, xciii, p. 246, 1902.

[2] *Arch. f. d. ges. Physiol.*, cvii, p. 252, 1905.

ability of the membrane.[3] The following simple experiment seems to support this view. If we put the eggs of *Fundulus* (about three days after fertilization) into a test-tube filled with a 3 M solution of NaCl, the eggs will float at first but sink after about three to six hours. In a $\frac{10}{8}$ M solution of $CaCl_2$ they will float for about half an hour. But if we put the eggs into a mixture of 50 cc. 3 M NaCl + 1 cc. $\frac{10}{8}$ M $CaCl_2$ they will float three days or more.[4] The interpretation of this experiment seems to be as follows: The membrane of the egg of *Fundulus* is impermeable for water as well as for salts, and since the interior of the egg contains a liquid of a considerably lower specific gravity than that of a 3 M solution of NaCl or of a $\frac{10}{8}$ M solution of $CaCl_2$, the egg will float in such solutions and will continue to do so as long as these solutions cannot enter the egg; that is to say, as long as the membrane is entirely or nearly intact. When exposed to a 3 M solution of NaCl or to a $\frac{10}{8}$ M solution of $CaCl_2$, each one of these solutions will in a short time alter the membrane of the egg, the $CaCl_2$ more rapidly than the NaCl, so that the membrane loses its impermeability to salts. The outside solution now diffuses into the egg, whereby the specific gravity of the egg increases and it sinks. The addition of a small amount of $CaCl_2$ to the 3 M NaCl solution prevents or retards this destructive action of the salt upon the membrane.

The next question which presents itself is: How does the addition of a small amount of $CaCl_2$ inhibit the injurious action of the pure solution of NaCl upon the membrane? The writer had found that bivalent (or polyvalent) cations had an antagonistic action upon the various salts with monovalent cations, while the bivalent or polyvalent anions had no antagonistic effect, and he called attention to the analogy of this observation with the effect of ions upon the precipitation of colloids. Negatively charged colloids can be precipitated by cations but not by anions, and the precipitating efficiency of the bivalent cations is consider-

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[3] A. P. Mathews suggested in the same year the opposite view; namely, that the membrane is impermeable for a pure NaCl solution, while the addition of $CaCl_2$ renders it permeable. He explains the death of the egg in a pure NaCl solution as due to the loss of water on the part of the egg caused by the hypertonic character of the solution (A. P. Mathews: *Amer. Journ. of Physiol.*, xii, p. 419, 1905). As a matter of fact, however, a $\frac{M}{2}$ solution of NaCl is not hypertonic for the egg of *Fundulus*; and, moreover, the membrane of the egg is impermeable for water.

[4] Loeb: *Biochem. Zeitschr.*, xlvii, p. 127, 1912.

ably greater than that of the monovalent cations. We might then expect that the salts influence a colloid in the egg membrane, and this inference seems to be in agreement with all the facts.

A further tentative assumption was that the two oppositely charged ions influence the colloid of the membrane in an opposite sense. If, therefore, a trace of a salt with a bivalent metal like $CaCl_2$ renders a salt with a monovalent metal like NaCl harmless, then on this assumption the injurious action of NaCl was due to the Cl ion, and the corrective effect to the Ca ion. Such an assumption was made by the writer as well as by A. P. Mathews.[5] But there were facts which it was impossible to reconcile with such a view, as, for instance, that there was some antagonism between $SrCl_2$ and $MgCl_2$.[6] In each of these salts the effect of the cations prevails to such an extent over that of the anion that their antagonism can not be explained on the assumption that it is based on the action of the oppositely charged ions. This and other facts induced the writer to question the correctness of the view that antagonistic salt action is due to an antagonism between oppositely charged ions, and he has recently been able to show that the toxicity of NaBr, Na_2SO_4, $NaNO_3$, and other sodium salts for the adult fish of *Fundulus* can be abolished through the addition of NaCl, and other chlorides, but not by other sodium salts.[7] In this case, there could be no doubt that the toxic effects of certain anions could be counteracted through the addition of another anion; namely, Cl. It was also found that this effect was specific, since no other anion but Cl acted in this way.

This and similar facts suggested to the writer a different explanation of antagonistic salt action, which may be briefly designated as the idea that the mixture of $NaCl + KCl + CaCl_2$, in the right proportion and concentration, has a specific membrane-forming or membrane-preserving effect upon all cells; while solutions different from this mixture have a destructive effect which is the higher, the higher its concentration and the more the solution deviates from the mixture $NaCl + KCl + CaCl_2$.

However, these experiments had not been made on the eggs of *Fundulus*, which are the most favorable object for experiments on

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[5] Loeb: *Amer. Journ. of Physiol.*, vi, p. 411, 1902; Mathews: *ibid*, xi, p. 455, 1904.

[6] Loeb: *loc. cit.*

[7] *Biochem. Zeitschr.*, xliii, p. 181, 1912.

the antagonistic action of salts. It seemed, therefore, necessary to find out whether there is any evidence in support of the view that antagonistic salt action in the case of the eggs of Fundulus is due to an antagonism between oppositely charged ions.

II.

In the new experiments we shall have to make use of a determination of that concentration of the chlorides of the alkaline metals and the metals of the alkaline earths which is just sufficient to prevent the formation of an embryo. Distilled water is, as we stated, harmless for these eggs and so are the solutions of any salt below a certain limit; that means in such solutions all the eggs can form embryos. Above that limit, the percentage of eggs which can form embryos becomes smaller and smaller until finally a concentration is reached at which no egg is able to form an embryo. We call this limit the toxic concentration.

TABLE I.

Toxic concentrations of chlorides.

$LiCl$	$>\frac{6}{32}$ M $<\frac{7}{32}$ M	$BeCl_2$	? * M
$NaCl$	$\frac{16}{32}$ M	$MgCl_2$	$\frac{10}{32}$ M
KCl	$>\frac{22}{32}$ M $<\frac{24}{32}$ M	$CaCl_2$	$>\frac{5}{32}$ M $<\frac{6}{32}$ M
$RbCl$	$>\frac{24}{32}$ M $<\frac{28}{32}$ M	$SrCl_2$	$>\frac{12}{32}$ M $<\frac{13}{32}$ M
$CsCl$	$>\frac{12}{32}$ M $<\frac{16}{32}$ M	$BaCl_2$	$>\frac{7}{32}$ M $<\frac{8}{32}$ M

* $BeCl_2$ forms strongly acid solutions which kill the eggs in very low concentrations. The toxic agent in this case is, however, the acid and not the $BeCl_2$.

If the antagonistic action of two salts is due to an antagonism between the ions of opposite sign, we are compelled to assume that such an antagonism exists also between the oppositely charged ions of the same salt; *e.g.*, between Na^+ and Cl^- in the case of NaCl. On the basis of that assumption we should conclude that the two opposite ions balance each other better in a KCl or RbCl solution than in a solution of LiCl or NaCl, since Table I shows that the former are less toxic than the latter. This fact might be intelligible on the assumption that Cl is the toxic ion since K and Rb are more electropositive than Li and Na. Yet it can be shown that the difference of toxicity between the various chlorides can not be explained on the assumption of an antagonism between the oppositely charged ions of the same salt.

The writer had shown in his previous researches that if NaCl (or any other of the chlorides of this series) reaches a toxic concentration, the addition of a trace of $CaCl_2$ (or of many other salts with a bivalent metal) may render the solution harmless. On the assumption of an antagonism between the oppositely charged ions and of the toxicity of the anion, this would mean that the toxic action of Cl is incompletely balanced by the ions of Li, Na, etc., and that the trace of Mg, Ca, etc., is required to counteract the excessive action of the Cl ions. It would, moreover, be necessary to assume that this excess of the action of Cl would become greater the higher the concentration of the solution, since with increasing concentration of a salt its toxicity increases. It would follow from this, that through the addition of $CaCl_2$ it might be possible to produce embryos in a relatively higher concentration of KCl and RbCl than of NaCl or LiCl, since the former salts are less toxic,—which in the terms of our assumption would mean better balanced in regard to the oppositely charged ions. It was first ascertained that through the addition of 1 cc. $\frac{M}{1}$ $CaCl_2$ to 50 cc. of a toxic concentration of LiCl, NaCl, etc., the maximum number of embryos can be obtained.

TABLE II.

CONCENTRATION OF SOLUTION	PERCENTAGE OF EGGS WHICH FORM EMBRYOS IN 1 CC. $\frac{M}{1}$ $CaCl_2$ + 50 CC.				
	LiCl	NaCl	KCl	RbCl	CsCl
$\frac{3}{8}$ M	100				
$\frac{4}{8}$ M	30	88			72
$\frac{5}{8}$ M	2	92	87	96	
$\frac{6}{8}$ M	0	80	21	81	43
$\frac{7}{8}$ M		89	25	70	
$\frac{8}{8}$ M		93	7	18	1
$\frac{9}{8}$ M		76	0	9	
$\frac{10}{8}$ M		64		0	
$\frac{11}{8}$ M		93			
$\frac{12}{8}$ M		51			
$\frac{13}{8}$ M					
$\frac{14}{8}$ M		14			
$\frac{15}{8}$ M		0			
$\frac{16}{8}$ M		0			

The experiment with CsCl was not repeated and must therefore be left out of consideration.

It is obvious that the maximal concentration in which eggs can still form embryos is highest in the case of NaCl, where it is $\geqq \frac{14}{8}$ M, which is enormous. (It may be mentioned incidentally that this would be inconceivable if the eggs were permeable for a mixture of NaCl + $CaCl_2$, as Mathews assumes, since the fish after hatching cannot live in a solution above $\frac{9}{8}$ or possibly $\frac{10}{8}$ M of NaCl + $CaCl_2$.)

If we compare the toxic limit of these salts with and without the addition of $CaCl_2$, we find the increase due to $CaCl_2$ as follows:

TABLE III.

	TOXIC LIMIT		
	Without Ca	With Ca	Increase in per cent
LiCl	$\frac{3}{16}$ M	$\frac{6}{8}$ M	400
NaCl	$\frac{16}{32}$ M	$>\frac{14}{8}$ M	350
KCl	$\frac{22}{32}$ M	$\frac{8}{8}$ M	50
RbCl	$\frac{24}{32}$ M	$\frac{9}{8}$ M	50

If the toxicity of LiCl, NaCl, KCl and RbCl were due to an excess of the action of the Cl ion over the cation; and if the Ca ion served to counteract the effects of the Cl ion, we should expect that through the addition of Ca the toxicity of KCl and RbCl would be raised at least in the same proportion as that of NaCl or LiCl; while in reality it can only be increased to $\frac{1}{8}$ or $\frac{1}{7}$ of that proportion. This means that the assumption that the toxicity of these salts is determined by an (incomplete) antagonism between the oppositely charged ions, the Cl ion being the toxic ion, is wrong or inadequate.

III.

While there may be uncertainty as regards the question whether in the case of a toxic concentration of NaCl the toxicity is due to the Na^+ or to the Cl^- ion or to the molecule, there is less uncertainty in the case of $CaCl_2$ and the other chlorides of the alkaline earth metals. In their case the toxicity must be due to the cation or to the molecule on the basis of the following consideration. The toxic concentration of $CaCl_2$ is between $\frac{5}{32}$ and $\frac{6}{32}$ M. Since this is less than half the toxic concentration of NaCl, KCl, or RbCl, and since the toxicity of these latter salts is diminished or annihilated through the addition of Ca, it is impossible to ascribe the high toxicity of $CaCl_2$ to anything but the cation or the molecule, even if we were willing to admit that the toxicity of NaCl were due to the Cl ion.

A similar reasoning holds for $MgCl_2$, $SrCl_2$, and $BaCl_2$. The toxic concentration of $MgCl_2$ is $\frac{10}{32}$ M. We shall see later that even a $\frac{10}{8}$ M NaCl solution can be antagonized by the addition of 4 cc. $\frac{M}{1}$ $MgCl_2$, and we are certain that the antagonistic action in this case is due to the Mg. Hence, if we find that a pure $\frac{10}{32}$ M solution of $MgCl_2$, is already toxic, we can say that any toxic effect the Cl ions might have in this solution would be more than compensated by the Mg ions present (if we assume temporarily that the two ions are mutually antagonistic). Hence the toxicity of a $\frac{10}{32}$ M $MgCl_2$ solution cannot be due to the Cl ion, but must be due to the Mg ion or the $MgCl_2$ molecule. A similar reasoning applies to $SrCl_2$ and $BaCl_2$.

These salts with a bivalent cation furnish us, therefore, with a safer basis for the investigation of the question whether the antagonism between two salts exists necessarily between two ions of opposite charge than do the salts with a monovalent cation, like NaCl, where we cannot tell with certainty which of the two ions is the toxic one. If the antagonism between two salts were necessarily due to an antagonism between oppositely charged ions and if the antagonistic salt action followed exclusively the laws of the precipitation of colloids, we should expect that where the cation is the toxic agent it should be more efficiently antagonized by a salt with a polyvalent anion than with a monovalent anion, since the precipitating efficiency of ions upon colloids increases rapidly with the valency of the ion. If, therefore, the toxicity of a pure $\frac{10}{32}$ M solution of $MgCl_2$ is due to the Mg ion, it should be easier to antagonize this solution with sodium sulphate or sodium citrate than with sodium chloride. The experiments of Table IV show, however, that there is hardly any difference between the antagonistic effect of these three salts. The method of procedure is as follows: The toxic concentration of $MgCl_2$ used was a $\frac{5}{16}$ M solution in which the newly fertilized eggs of *Fundulus* can, as a rule, no longer develop. As antagonistic salts, sodium chloride, sodium acetate, sodium sulphate, and sodium citrate were used. The $\frac{5}{16}$ M $MgCl_2$ solution was made up with the antagonistic salt solution (instead of with distilled water), so that the concentration of $MgCl_2$ was the same in each solution, namely, $\frac{5}{16}$ M; while 50 cc. of this solution contained varying quantities of the antagonistic salt.

TABLE IV.

ANTAGONISTIC SALT	PERCENTAGE OF EGGS WHICH FORMED EMBRYOS IN 50 CC. $\frac{5}{16}$ M $MgCl_2$ CONTAINING IN ADDITION														
	0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0	10.0	12.0	15.0	20.0
	CC. OF ANTAGONISTIC SALT														
$\frac{M}{1}$ NaCl	0	5	21	20	36	45	46	52	70	70	81	59	50	77	
$\frac{M}{1}$ Na acetate	0	18	23	43	32	42	39	30	60	45	53	40	34	46	
$\frac{M}{2}$ Na_2SO_4	0	14	30		46		70	64		76	71	75	80	87	73
$\frac{M}{2}$ Na citrate	0	12	15		50		63	77		66	54	57	28	25	4

The difference in the antagonistic action of these four salts observed in Table IV is within the limits of error and individual variation. This proves that the antagonization of the toxic effects of a cation is in this case not caused by an anion but by a cation or by the molecule. This fact has an important bearing on the writer's former observation that a toxic concentration of NaCl could be antagonized by bivalent or polyvalent cations, but not by bivalent or polyvalent anions. This appeared at that time as an argument in favor of the idea that the toxic action of NaCl was due to the anion. We now find that in a case in which the toxic agent is surely not an anion, but either a cation (Mg) or a molecule, the same law prevails; namely, that the valency or nature of the anion has practically no influence upon the antagonistic efficiency of a salt. We can, therefore, not use the inefficiency of anions in a case of antagonistic salt action as an argument in favor of the assumption that the toxic agency in such a case must be an anion. If the antagonistic action of the sodium salts against $MgCl_2$ was not due to the anion, it must have been due to the cation, namely, Na, or to the molecule.

We can show that the toxic limit of a $MgCl_2$ solution can be raised by other chlorides much more efficiently than by NaCl. We have seen that in a $\frac{10}{32}$ M solution of $MgCl_2$ as a rule the newly fertilized egg of *Fundulus* does not live long enough to form an embryo. The question presented itself: By which type of salts can we raise the toxic limit of $MgCl_2$ more effectively, by Na salts with polyvalent anions, or by chlorides of different metals? The experiments showed that the latter was the case.

Newly fertilized eggs of *Fundulus* were put into solutions each containing 50 cc. $\frac{10}{32}$, $\frac{11}{32}$, and $\frac{12}{32}$ M $MgCl_2$ containing varying amounts of sodium citrate or of KCl. It was found that the addition of sodium citrate did not allow the eggs to develop in a $MgCl_2$ solution above $\frac{10}{32}$ M, while with the addition of KCl some eggs could still develop in $\frac{12}{32}$ M $MgCl_2$.

TABLE V.

Percentage of embryos formed in 50 cc. $MgCl_2$ *in which were contained varying quantities of* KCl *or of sodium citrate.*

CONCENTRATION OF $MgCl_2$	0	0.5	1.0	2.0	4.0	6.0	0	2	4	8
	CC. $2\frac{1}{2}$ M KCl						CC. $\frac{M}{2}$ SODIUM CITRATE			
$\frac{10}{32}$ M	0	18	30	55	8	0	0	2	9	13
$\frac{11}{32}$ M	0	1	18	32	5	0	0	0	0	0
$\frac{12}{32}$ M	0	1	0	0	0	0	0	0	0	0

The slight antagonistic effect of sodium citrate in Table V was due to the Na ion and not to the citrate ion, since we have seen in Table IV that NaCl acts in the same way. It would be of the greatest theoretical importance to find other cases in which a cation is both the toxic as well as the antagonistic agent. It would deprive us of the excuse for arguing that because Ca antagonizes NaCl, the toxicity of the latter must be due to the anion. This proof will be given in the next section.

IV.

In one of his earliest papers on salt action, the writer had already shown that a toxic solution of $CaCl_2$ could be antagonized by KCl and NH_4Cl, but not by NaCl and LiCl. Since we now are certain that the toxicity of $CaCl_2$ is not due to the anion but to the cation, the question whether cations can antagonize the toxic action of other cations became of interest. For this reason, experiments like those of Table V were carried on with toxic solutions of $MgCl_2$, $CaCl_2$, $SrCl_2$, and $BaCl_2$. It was found that a $\frac{5}{16}$ M solution of

$MgCl_2$ could be antagonized by NaCl, KCl, RbCl, CsCl, and NH_4Cl, but not by LiCl; $CaCl_2$ could be antagonized by KCl, RbCl, CsCl, and NH_4Cl, but not by LiCl and NaCl; $SrCl_2$ could be antagonized by NaCl, KCl, and RbCl, but not by LiCl; and $BaCl_2$ by LiCl, NaCl, KCl, RbCl, CsCl, and NH_4Cl. The results are set forth in Tables VI to IX.

TABLE VI.

ANTAGONISTIC SALT	PERCENTAGE OF EGGS FORMING EMBRYOS IN 50 cc. $\frac{5}{16}$ M $MgCl_2$ CONTAINING IN ADDITION					
	0	0.5	1.0	2.0	4.0	6.0 cc. $2\frac{1}{2}$ M
	ANTAGONISTIC SALT					
LiCl............	0	0	0	0	0	0
NaCl...........	0	13	36	40	41	22
KCl............		10	60	62	46	19
RbCl...........		40	41	30	0	0
CsCl............		18	27	10	0	0
NH_4Cl..........		10	44	6	0	0

TABLE VII.

ANTAGONISTIC SALT	PERCENTAGE OF EGGS FORMING EMBRYOS IN 50 cc. $\frac{3}{16}$ M $CaCl_2$ CONTAINING IN ADDITION					
	0	0.5	1.0	2.0	4.0	6.0 cc. $2\frac{1}{2}$ M
	ANTAGONISTIC SALT					
LiCl............	0	0	0	0	0	0
NaCl...........	0	0	0	0	0	0
KCl............	0	15	9	21	37	45
RbCl...........		5	8	11	33	18
CsCl............		0	12	15	6	?
NH_4Cl..........		0	0	3	5	9

TABLE VIII.

ANTAGONISTIC SALT	PERCENTAGE OF EGGS FORMING EMBRYOS IN 50 cc. $\frac{13}{32}$ M $SrCl_2$ CONTAINING IN ADDITION					
	0	0.5	1.0	2.0	4.0	6.0 cc. $2\frac{1}{2}$ M
	ANTAGONISTIC SALT					
LiCl............	0	0	0	0	0	0
NaCl...........		0	3	3	12	10
KCl............		1	10	20	18	4
RbCl...........		0	4	7	2	0

TABLE IX.

ANTAGONISTIC SALT	PERCENTAGE OF EGGS FORMING EMBRYOS IN 50 cc. $\frac{5}{32}$ M $BaCl_2$ CONTAINING IN ADDITION					
	0	0.5	1.0	2.0	4.0	6.0 cc. $2\frac{1}{2}$ M
	ANTAGONISTIC SALT					
LiCl	0	8	12	22	4	0
NaCl		0	0	8	9	0
KCl		5	3	11	10	22
RbCl		3	0	13	18	5
CsCl		4	4	28	25	1
NH_4Cl		36	60	57	5	0

The very powerful action of NH_4Cl against $BaCl_2$ was confirmed in other experiments. They suggest a specific action of the various salts.

In view of these results it is no longer surprising that we should also find some antagonism between two salts with bivalent cations and the same anion. Such observations would remain a riddle if we considered antagonistic salt action as necessarily due to oppositely charged ions. It is difficult to show that the toxic action of $CaCl_2$ is antagonized as well by KCl as by potassium citrate or sulphate, on account of the precipitate formed. The experiments with $MgCl_2$ given in Table IV, however, serve this purpose.

V.

The results of this paper harmonize with the conclusions at which the writer arrived in his more recent studies on the same subject.[8] If it is true that the injurious action of a single salt in a sufficiently high concentration consists in an alteration of the membrane. the antagonistic salt action consists in a diminution or prevention of that alteration. In a mixture of NaCl + KCl and $CaCl_2$ in the right concentration the membrane lasts the longest and we may understand that the egg can resist a higher concentration of a mixture of NaCl + $CaCl_2$ than of KCl + $CaCl_2$ or RbCl + $CaCl_2$ or of LiCl + $CaCl_2$, for the simple reason that NaCl + $CaCl_2$, in the proportion of 50 cc. NaCl to 1 cc. or less $CaCl_2$, comes nearer the optimal mix-

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[8] *Biochem. Zeitschr.*, lxvi, p. 270, 1914.

ture $NaCl + CaCl_2 + KCl$ in that proportion in which these salts exist in the sea water, than any other combination of two salts in the same proportion.

On the basis of this argument we should expect that $CaCl_2$ is able to antagonize a higher concentration of NaCl than either $MgCl_2$ or $SrCl_2$ or $BaCl_2$. Experiments made to establish the highest concentration of the combination of NaCl with the chlorides of Mg, Ca, Sr, and Ba, in which newly fertilized eggs are able to form an embryo gave the following result.

TABLE X.

Highest concentration of NaCl *solutions in which the newly fertilized eggs of Fundulus can still form an embryo.*

50 cc. $\frac{10}{8}$ M $NaCl + 4$ cc. $\frac{M}{1} MgCl_2$
50 cc. $\frac{14}{8}$ M $NaCl + 1$ cc. $\frac{M}{1} CaCl_2$
50 cc. $\frac{11}{8}$ M $NaCl + 1$ cc. $\frac{M}{1} SrCl_2$
50 cc. $\frac{7}{8}$ M $NaCl + 1$ cc. $\frac{M}{1} BaCl_2$

The difference is striking and easily understood on the assumption that the combination $NaCl + CaCl_2$ is a nearer approach to the mixture $NaCl + KCl + CaCl_2$ than any of the other combinations mentioned in the table.

The question may then be asked: Why can we substitute even to some extent Mg or Sr or Ba (or Pb and Zn) for Ca? The answer must be that all these metals must have one property in common with Ca, which is of importance for the preservation of the membrane, and this property may well be the formation of a membrane of precipitation at the surface of the egg, as Traube's theory would demand. It is very likely that the same membrane-forming substance of the cell which is precipitated by Ca is also precipitated by Mg, Sr, Ba, and other bivalent metals. That these metals are not as satisfactory as $CaCl_2$ may be due to the fact that the calcium precipitate has certain physical properties which are not shared by the precipitates with other metals.

The writer had called attention to the fact that the difference in the action of Na, K, and Ca upon the absorption of water in muscle resembled the influence of the same ions on the absorption of water by soaps;[9] and Hansteen Cranner[10] has shown that the

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[9] Loeb: *Arch. f. d. ges. Physiol.*, lxxv, p. 303, 1899.

[10] *Jahrbücher f. wissensch. Botanik*, liii, p. 536, 1914.

same difference exists for the absorption of water by the roots of plants as well as by the isolated membranes of plant cells. Ca forms solid soaps, and Robertson has pointed out that the fact that so little Ca is needed for its antagonistic action harmonizes with the assumption that its action depends upon the formation of a precipitate.[11]

A complete theory of antagonistic salt action may also have to consider the fact that the cell walls consist of more than one chemical compound. As far as plant cells are concerned we know that this is true, since they contain aside from cellulose and pectine substances also fatty acids (not lecithin), as Hansteen Cranner[12] has recently shown.

The experiments of Beutner and the writer on the origin of electrical phenomena in animals have also led to the conclusion that the surface of the cell contains higher fatty acids or other water-immiscible substances.[13] The bulk of the cell wall must be of a different chemical character. The fact that the importance of the membrane of animal cells has so long been underestimated has left a gap in our knowledge of this organ, and this prevents us from formulating a complete theory of antagonistic salt action. Whatever this theory may be in detail, we may be sure that the facts of antagonistic salt action cannot be expressed by the assumption that it is based upon the action of oppositely charged ions.

SUMMARY.

1. The main object of this paper is an investigation of the question whether antagonistic salt action is based on an antagonism between oppositely charged ions. It is shown that this assumption leads to difficulties if applied to the antagonization of a toxic salt with a monovalent cation by a salt with a bivalent cation.
2. It is shown that for the toxic concentrations of $MgCl_2$, $CaCl_2$, $SrCl_2$, and $BaCl_2$ the cation is the toxic agency; and that, nevertheless, the efficiency of their antagonists is determined by the cation and not by the anion.

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[11] T. B. Robertson: *Ergeb. d. Physiol.*, x, p. 216, 1910.

[12] *Loc. cit.*

[13] Loeb and Beutner: *Biochem. Zeitschr.*, li, p. 288, 1913; lix, p. 195, 1914.