ON DEFENSE RUPTURE AND THE ANTAGONISTIC ACTION OF SALTS

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In a recent number of this *Journal*[1], I have pointed out that the well-known antagonistic action of Ca to Na, was probably at the bottom of the peculiar "defense rupture" action of Ca, as described by Bullock and Cramer[2], in relation to infection with the organisms of gas gangrene.

In the preceding number of this *Journal*, Cramer and Gye[3] give some additional experiments, which they claim demonstrate that the matter is not so straightforward and simple.

In these new experiments it is shown that if the gas gangrene organisms or their spores are washed in Ringer's solution instead of NaCl, they are unable to kill the mice into which they are injected. Obviously here it is not a question of the unbalanced action of the Na playing a part in the question.

It is now clear from these experiments and also from other results obtained by Cramer and Gye, published since the appearance of my original paper, that these authors are dealing with a much more complicated series of events than at first seemed apparent. Two widely different salt actions enter into the problem.

First, the antagonistic action of Ca-ions to the Na-ions on the bacteria, such as I have described in my paper. Secondly, a defense rupture action as these authors call it, of the Ca-ions and numerous other poisonous substances on the tissues of the animals, in the absence of which the gas gangrene organisms are wholly unable to set up infection in the animals into which they are inoculated.

If the emulsions of gas gangrene organisms employed are free from spores, the effect will be as I have described in my experiments with *B. anthracis*. The bacteria will be killed by the NaCl or their powers of resistance so lowered that the leucocytes soon get rid of them when they are injected into the animal. If a little Ca is added to the emulsion just before injection, and the action of the NaCl has not been too prolonged, the bacteria will recover their normal condition, and as the Ca also devitalizes the tissues of the animal at the point of injection, infection will occur. On the other hand if the action of the NaCl

[1] Shearer (1919), *Journ. Hyg.* XVIII. 337.
[2] Bullock and Cramer (1919), *Proc. Roy. Soc.* Ser. B. xc. 513.
[3] Cramer and Gye (1920), *Journ. Hyg.* XVIII. 463.

on the bacteria has been too prolonged, then the addition of the Ca will not produce infection, as the bacteria will be either dead or so far injured by the NaCl as to be passed restoration.

If spores are present these will be able to resist the action of the NaCl in virtue of their peculiar structure, the addition of Ca will bring about defense rupture action, and it will not matter much if the Ca is injected into the animal at the same time as the spores or much later, as the spores can probably remain alive in the body for long periods. The proper conditions are prepared for their development through the injection of Ca or any other injurious substance that will produce defense rupture.

I have shown in conjunction with Crowe[1], that the meningococcus can be taken up by leucocytes, but that if these are crushed up seven or eight hours later and the bacteria liberated once more, they are still capable of growth and reproduction. Leucocytes can take up bacteria without being able in all cases to kill and immediately digest them. In the light of this fact, we may conclude that spores with their impervious[2] cell walls survive the attack of the leucocytes and their digestive ferments for a much longer period than vegetative forms of bacteria. Their small size moreover allows of their being readily transported to all parts of the body. We can understand how they may set up an infection at a point where the Ca is injected into the animal ten days after this animal had received the spores themselves.

The difficulty of getting a clear grasp of the relationships of this problem of infection to the gas gangrene organisms in all its aspects, it seems to me is greatly increased in attempting to work it out using spores and vegetative forms of bacteria together. If either are used alone more progress could be made with its solution. In this work of Cramer and Gye, it seems to be forgotten that Ca after all is a violent local poison to the tissue cells of most animals. It is possible to produce abscess formation in many animals with considerable rapidity by the injection of weak solutions of $CaCl_2$ in the complete absence of any specific germs. Moreover these authors seem to have surrounded the whole question of the defense rupture action of Ca on the tissues with a certain degree of mystery that is much to be regretted; resolved into its component factors the problem is clear and straightforward.

I have shown that the lethal action of Ca on the cell is irreversible and signifies the commencing death of the cell. The action of NaCl on the other hand is reversible within quite wide limits. The death of the cell in this case takes place very slowly and is due to the diffusion of the salts from the cell; as the cell wall after treatment with a weak but pure solution of NaCl immediately becomes permeable to the free ions in the cell. It is the loss of

[1] Shearer and Crowe (1917), *Proc. Roy. Soc.* Ser. B. LXXXIX. 440.

[2] As illustrating the impermeable character of the spore wall, it is worth recalling Buchner's early observation, where he claimed to have germinated the spores of *B. subtilis* after these had been treated with concentrated sulphuric acid. (See Buchner, "Ueber das Verhalten der Spaltpilzsporen gegen Anilinfarbstoffe," *Aertzlich. Intelligenzbl.* 1884.)

these salts from the cell, that brings its life to an end[1]. If this diffusion is stopped by transferring the cell to a balanced solution or by the addition of a little Ca to NaCl, then the cell recovers its normal condition, if its loss of salts has not been too great. In distinction to this action that of Ca is final once it has commenced and no recovery is possible[2].

[1] Since my paper appeared, a clear demonstration of this effect has been described by Gray (*Journ. Physiol.* 1920, LIII. p. 308) in the trout egg. Injury of the cell membrane, whether mechanical or through the poisonous action of salts, immediately renders this membrane permeable to the contained electrolytes of the cell, and the loss of these brings about the precipitation of the globulins of the egg with death; during life these are held in solution by the contained neutral salts.

[2] The recent work of Brooks (*Journ. Gen. Physiol.* 1918–20) on the effect of different electrolytes on the respiration of *B. subtilis* has shown that the action of NaCl and CaCl in affecting respiration is very similar to that demonstrated by the conductivity method as described in my paper.

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