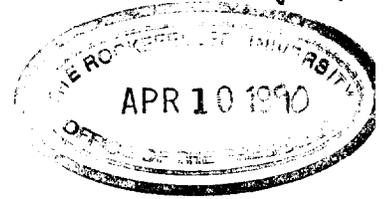


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*x of saline, dehydrated  
cholera, Marty Kaplan*



April 4, 1990

Dear Dr. Lederberg

I apologize for the delay in answering your letter of February 17, but want, first, to thank you for all the trouble that you went to in trying to chase down the VanSlyke reference. Since receiving your letter I have made additional attempts on my own, but without success. To clarify things, let me explain the background a bit further.

About 10 years ago I had some correspondence with Baird Hastings about the early studies on Acid-Base and in a memo that he had prepared some years before he mentioned a national

meeting in which the work of VanSlyke, Wu and McLean had been presented. This work had been done in China in the early '20's. According to Hastings, the discussion was dominated by some scathing remarks made by Dr. Peters from Yale. I was under the impression that the discussion had been published. It is well known that Peters had a rather sharp tongue. But I was more interested in the substance of his objections. All the analyses had been done on blood taken from a single Manchurian horse, and I wondered whether Peters was objecting to applying conclusions derived from horses to the situation in man, or whether from a statistical point of view he was objecting to the use of just a single animal (n=1, etc). It's a very minor point and one that can't be chased down further. Merely as an aside I have often been impressed by the paucity of statistical analysis that has characterized many of the most important discoveries in biochemistry. I am not over fond of statistics myself but grudgingly grant them their importance.

Many thanks for the reprint from Academic Medicine edited by John Bowers. I agree with so many of the points you have made that it would take far too long to comment on them. You ask specifically about the background of saline as a therapeutic agent. I have been interested in this for quite a while and actually in 1971 sponsored a medical student named Marty Kaplan to go to London, work in the British Museum, and see what he could find about the early days of saline, particularly the midpart of the 19th century. He wrote an excellent report which I enclose and had intended to expand and then publish. I knew of no previous historical treatment. As luck would have it, at exactly that time an excellent article appeared by Norman Howard-Jones, and there was little that we could add to it so we gave up the idea. However here is a brief summary along with some key references. I definitely would incorporate the history of cholera and saline into any history of acid-base.

*Kaplan memo.*

I don't think that saline appears in the medical literature before about 1820. At that time cholera escaped from the Indian subcontinent and struck Europe, first in Russia and by 1831 in France and England. There is an early report from Dr. Hermann in Moscow based on chemical analyses that the tissues in cholera had lost fluid. Dr. O'Shaughnessy was from London and went to Newcastle to study the cholera and made some chemical analyses of the blood from cholera victims. He concluded that "blood had lost a large part of its water...and of the free alkali contained in the healthy serum not a particle is present in some cases." This is a landmark in clinical investigation. A brief summary was printed in the Lancet, a more detailed report subsequently appeared in a printed pamphlet.

A Scottish physician, Dr. Latta, read O'S's paper and as a result tried saline in a number of cases. The initial effect was often dramatic, but the overall mortality was not greatly lowered. In part this was undoubtedly due to the sepsis produced by the non-sterile infusions, and in part also from the fact that the infusions had not been administered for a sufficiently long period of time after the vomiting and diarrhea had ceased. In other words, the infusions were given in a large initial dose and then stopped.

A number of British physicians followed Latta's lead and tried saline, but again with disappointing results. Also there were many doctors who were completely opposed to such a radical idea. By about 1860 the literature on saline seems to have dwindled away. In 1874 there was a report by Fogge from Guy's on the treatment of a single case of diabetic coma treated with just saline, and with either transient or complete recovery, I can't remember which. The important thing is that the rationale for this treatment was based on the prior experience with the dehydration of cholera.

What happened between about 1870 and 1900 I do not know, but I plan to go back through the Lancet to see if there are any hints. Both Kaplan and Howard-Jones concluded that sepsis produced by the non-sterile infusions was the major stumbling block. Saline was then introduced in the tropics about 1905 and the acidosis aspects of tropical disease were studied by Sellards from the Johns Hopkins at about the same time.

In recent years the biochemical lesions have been well documented at the cellular and molecular biological levels. As you well know, the greatest advance in the treatment of cholera in the third world has been the introduction of fluids containing sucrose which may be taken by mouth. There is little doubt in my mind but that this follows from very basic studies on the co-transport of sodium and sugar by the intestinal epithelium. It's almost absurd to think that some pure water, a little common table salt and some sugar may be one of the most effective therapeutic agents of all time, at least as judged by

mortality rates in probably the most lethal of known epidemic diseases. I often wonder what would have happened if in the middle of the 19th century there had been an NIH and somebody had submitted a proposal to treat cholera with some sweetened salt water by mouth

Norman Howard-Jones. Cholera Therapy in the Nineteenth Century. *J. History of Medicine and Allied Sciences*. Vol. 27: 373-395, 18 1972.

Carpenter, Charles C.J. Treatment of cholera--Tradition and authority versus Science, Reason and Humanity. *Johns Hopkins Medical Journal*, 39: 153-162, 1978.

The Howard-Jones account is unbelievable. I had never before realized just what the medical profession was up to just about 150 years ago. At times it sounds like the worst of the SS concentration camps. Carpenter spent a good bit of time in Calcutta. There is a detailed publication of his studies in the *Bulletin of the Johns Hopkins Hospital*, 118: 165-243, 1966.

I have also enclosed the MS by Kaplan.

I plan to work on my little project in history for at least a year and see where I stand. One of the general issues that interests me particularly involves the period about 15 years either side of WW II when there is no doubt but that disputes over nomenclature had made the topic extremely difficult for medical students. The endless different graphs of the Henderson-Hasselbalch equation all showed exactly the same thing but each new one was claimed by its sponsor to be an advance in the graphic arts.

I was particularly interested in your comment about "the exposure of biological scientists to health problems". This is a difficult problem in the medical curriculum. I have had some thoughts ~~thoughts~~ about clinical and pre-clinical departments and if I ever get them better organized I will put them down on paper. I'll send along a copy.

With best regards and many thanks for your help.

Sincerely  
  
Gilbert H. Mudge MD