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“International Symposium on HCO_3^- and Cystic Fibrosis” Preface

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This symposium on the topic of HCO_3^- transport in cystic fibrosis (CF) was convened in San Diego, CA, on March 3-5, 2001, because of a perceived need to increase research efforts on the role of this anion in the pathogenesis of cystic fibrosis. Over the past two decades, great emphasis has been placed on abnormal management of Cl^- and Na^+ ions as a function of defective electrolyte transport in this hereditary disease. However, despite the facts that the disease takes its name from destruction of the pancreas and that the pancreas is <u>the</u> organ of HCO_3^- transport, few studies examining potential cellular defects in HCO_3^- transport in cystic fibrosis have been undertaken. In short, HCO_3^- has been a neglected ion.

Cystic fibrosis is the most common, lethal genetic disease affecting Caucasians. It appears as a recessive gene in about 4% of this population yielding an incidence of about 1 in 2,400 live births. We have known the sequence of the gene (cystic fibrosis transmembrane conductance regulator: CFTR) and the most common mutations for CF for more than a decade. Defects in this gene are best known to affect most exocrine gland tissues, but its expression is generally most morphologically devastating in the vas deferens, pancreas, and lung. The electrolyte transport of the sweat glands, salivary gland, gallbladder, biliary tree, and intestines are known to be defective as well, but structural changes are less pronounced or absent in these tissues because secondary inflammatory processes are less severe or absent. The inflammatory destruction appears to follow failure of the organ to properly secrete or modify fluids required to clear macromolecular products from the target organ. Thus, the sweat gland, which produces minor quantities of macromolecules, suffers no morphological compromise while the pancreas and inflamed lung, which produce large quantities of molecules, are eventually destroyed.

Indeed, the principal impetus for this conference took its roots in two early clinical studies, first by Hadorn *et al.* in 1963 [1] and later by Kopelman *et al.* in 1985 [2]. Both of these studies convincingly demonstrated that pancreatic HCO_3^- secretion is severely defective in CF patients. Using somewhat more sophisticated techniques and a larger number of patients, Kopelman made the important observation that normal or near normal trypsin activity was present in some patients who retained pancreatic sufficiency (i.e., did not require supplemental enzymes for adequate digestion), but their enzymes were secreted in significantly lower volumes of pancreatic juice with significantly lower levels of HCO_3^- output. These results are direct evidence of failure to transport HCO_3^- ion in this disease. It is likely that destruction of the pancreas results from autolysis by activated trypsinogen and other proteases and lipases while they are still in the pancreatic ducts. The lack of HCO_3^- to maintain a high pH to prevent pro-enzyme activation and the loss of normal volumes of pancreatic juice to rapidly flush enzymes from the pancreatic ducts is probably the primary cause of pancreatic failure in CF patients.

But why should we be interested enough in epithelial HCO_3^- transport in general in cystic fibrosis to convene an international symposium dedicated to it? Cystic fibrosis has now been defined in the medical literature for more than half a century. Despite centuries of man-years of work, the consensus opinion is that the only basic physiological defect apparently common to all cells with a mutation in a normally expressed CFTR gene is a loss of Cl^- permeability in the plasma membrane. This defect goes far in explaining the defect in CF sweat and sweat gland functions, but so far, it has left us without a clear understanding as to the role Cl^- plays in disrupting the function of other organs. In most other organs, especially in the lung - the principal source of CF morbidity and mortality - we have almost no knowledge of which cell types are critically affected, let alone, a firm proof of the basic mechanism(s) producing the pathology. All of this is to say that cystic fibrosis remains in dire need of a unifying hypothesis. Cl^- impermeability is likely to be a principal culprit in organ pathogenesis, but even that is not without question. To wit, a few mutations of CFTR cause CF, but apparently do not result in significant Cl^- impermeability (as least as indicated by the results of reported sweat tests). Thus, we are compelled to raise our view to the horizon and look for other compounding factors. Indeed, there is almost no end to the suggestions of potential involvements of CFTR in bringing about destruction. These range from altering vesicular trafficking to directly enhancing bacterial binding, not to mention the numerous ion channels that CFTR is reported to control or regulate. However, at least from my perspective, cystic fibrosis is first and foremost a disease of defective epithelial electrolyte transport, and it therefore seems most logical to search for, define, and fully explain the abnormalities associated with this fundamental activity as the focus for answering that primordial question of "what components and events link the mutation to the pathology".

Bicarbonate begs for attention in this pursuit. The view that cystic fibrosis is a disease of "thick, sticky mucus" is perhaps more commonly held than any other of its even more firmly established abnormalities. It is well documented that mucus, or at least what appear to be inspissated macromolecules, is associated with the anatomical pathology of most exocrine target tissues of the disease. It is not easy to understand how a defect in Cl^- transport would directly result in pathogenic changes in mucus properties. The simplistic interpretation is that failure to secrete fluids and abnormal absorption results in mucus stagnation and subsequent structural deterioration. But the fact that thermoregulatory sweating, salivary secretions, gastric and intestinal secretions, and perhaps tracheobronchial secretions in CF are "normal" or at least adequate to sustain physiological function, compels the question of whether this simplistic notion is adequate to explain the most serious components of CF pathology. On the other hand, mucus is secreted frequently, if not always, in the presence of significant HCO_3^-. Presumably, at least one essential reason for this coincidence is that protons exert pronounced effects on the physical properties of macromolecular polyelectrolytes in solution and that the presence of HCO_3^-, the major extracellular buffer, is required to maintain a pH compatible with physiological properties of these molecules (mucus). Thus, we can surmise that defects in the ability to control HCO_3^- appropriately during mucus secretion may have effects on its state much more far reaching than the simple loss of Cl^- dependent fluid secretion or altered Cl^- concentrations. In this regard, given the extraordinary importance of pH to biological processes, it becomes easy to speculate that other processes important to exocrine organ health could be compromised as well. More specifically, the ability of airway epithelia to respond effectively to the initial (and/or chronic) stages of infection may well be the victim of poor HCO_3^- management and, therefore, poor pH control.

Critics of this thinking argue that the study of HCO_3^- in CF will be of lesser interest until it can be shown that the pH of the airway surface fluids is abnormal. This view ignores a principal feature of this disease - that it is a disease of defective response. This property applies especially to fluid and electrolyte secretion. It has long been held that if the CF lung did not become infected (inflamed), it would not deteriorate. If true, it may be that in the "resting" state, the airway (and perhaps other target organs) may maintain parameters within normal limits. However, upon challenge with a pathogen or trauma, the normal response at the insulted site may fail, and secondary events then lead to chronic pathology. This scenario implies that it may be difficult to detect the crucial problem or abnormality by examining parameters (pH, HCO_3^-, composition, or even baseline immunological defense) during unstimulated quiescence. The defect would be seen most clearly, only when the tissue is challenged to respond in a way similar to that required for its physiological survival. The implications here are that studies of tissues in the "resting" state may be only partially informative, or possibly uninformative. True, it may be difficult to assay the defective response in CF without knowing the nature of the stimulus involved, but to argue that unless the pH of the "resting" state is abnormal, HCO_3^- transport is not abnormal in CF, seems misplaced.

Recently, a more studies have indicated HCO_3^- transport abnormalities in other organs affected in CF. For example, defective HCO_3^- transport has been reported in human biopsies of nasal mucosa, pancreatic duct, duodenum. It is reported to be abnormal in several organs of transgenic mice as well as; e.g., duodenum, jejunum, ileum, colon, and gallbladder. All of these abnormalities appear to involve defective HCO_3^- secretion. Unfortunately, the state of our knowledge of HCO_3^- transport in epithelia at large leaves us without an immediate explanation for the basis of these observed abnormalities.

In the past five years, several major findings of new component molecules involved in HCO_3^- metabolism have been presented. Some examples are several previously unknown Na^+/HCO_3^- cotransporters, a new Cl^-/HCO_3^- exchanger (DRA: down regulated in adenoma) and another putative anion exchanger (PAT1: putative anion transporter), numerous additional isoforms of carbonic anhydrases, a HCO_3^- conductive channel (CFTR), and even a HCO_3^- dependent adenylate cyclase. New data relevant to the function of HCO_3^- secretion have cast old models into doubt and stimulated new ideas and mechanisms for its transport. Much of this work was represented or at least touched on during the conference and is presented here as proceedings for a larger audience. Hence, we were motivated to convene this conference.

It is my sincerest hope that this conference and these proceedings will focus a critical, scientific audience on the potential importance of HCO_3^- in cystic fibrosis and lead to an understanding of its relevant normal function and its dysfunction in the disease. Toward that end, we attempted to assemble a group of scientists with exceptional expertise in the various aspects of HCO_3^- transport as well as investigators renowned for their knowledge of HCO_3^- abnormalities expressed in CF. We hope that the introductions of different minds, lines of thought, and expertise will be a seed from which a more complete understanding of the pathology of cystic fibrosis will grow to established fact.

Key words Antiporters; Bicarbonates; Carbonate Dehydratase; Cystic Fibrosis;

Epithelial Cells; Hydrogen-Ion Concentration; Ion Transport; Mucus; Sodium Bicarbonate

Abbreviations CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; DRA: down regulated in adenoma; NBC: sodium bicarbonate cotransporter PAT: putative anion transporter

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We owe much to Ms. Joanne Albrecht for the numerous communications with participants and the organizational details that were essential to completing this event, which she handled for months preceding the conference as well as for her tireless efforts during its occasion. We were also extraordinarily fortunate to have the assistance and talents of Ms. Adele Neves in making numerous arrangements that led to a program without flaw. We thank Mr. Kirk Taylor for his careful attention to equipment and audiovisual support that made the presentations timely and effective.

Above all, however, we thank the contributors and participants for their unstinting and unselfish efforts in bringing this conference to the cutting edge of this field. No words of appreciation can match the effort and time required for these scientists to prepare superb presentations, attend the conference, and prepare their contribution to these proceedings for the benefit of others who could not be accommodated and for the public at large. Obviously, the success of any conference cannot exceed the quality of its contributors. I hope that by this standard alone both, the participants and the audience at large, will judge this symposium to be of the greatest success.

I would like to make a special note of appreciation to Dr. Michael Romero, who at the last moment was unable to attend the conference, but nonetheless prepared an excellent contribution on NBC (sodium bicarbonate cotransporter) exchangers, which is included in these proceedings herewith.

Personally, I would like to sincerely thank my wife, Dr. Liesbet Joris-Quinton, not only for putting up with me and my compulsive neurosis during the months of preparation for the conference, but especially for single handedly organizing and catering a delightful dinner for all the participants in order to help us stay within the limits of our finances. She was as effective as she was courageous.

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References

1. Hadorn B, Zoppi G, Shmerling DH, Prader A, McIntyre I, Anderson CM. Quantitative assessment of exocrine pancreatic function in infants and children. J Pediatr 1968; 73:39-50.

2. Kopelman H, Durie P, Gaskin K, Weizman Z, Forstner G. Pancreatic fluid secretion and protein hyperconcentration in cystic fibrosis. N Engl J Med 1985; 312:329-34. [85111006]