workshop b2: saturday, march 11

CF 2000

CF population screening 2000: The end is near. D.R. Witt. Kaiser Permanente Medical Care Program Northern California, San Jose, CA.

Since the discovery of the cystic fibrosis (CF) gene in 1989, the issue of population screening for CF has remained controversial. Nevertheless, the incorporation of screening into clinical practice is increasingly common. We are witnessing the final phase of the evolution of CF screening as widespread acceptance occurs and implementation becomes the focus. This presentation will not concentrate on whether or not there should be screening but rather on how we came to this point over the last eleven years, what is being done to foster the final stage of implementation, and what barriers remain. The presentation will include a brief historical overview of the major conferences and policy statements that have influenced screening, a synopsis of the major concerns about screening and evidence-based data that addresses them, and the status of the joint working group on CF screening. Data will also be presented from the Kaiser Permanente Northern California Cystic Fibrosis screening program demonstrating the results from a large, centralized, structured screening program. Issues to be addressed include pre-test education, incorporation of CF screening into counseling and testing for other genetic diseases, and program logistics from the clinical and laboratory perspective.

Gene Therapy and Future Directions in the Treatment of Cystic Fibrosis.. Wanda O'Neal, PhD, CF/Pulmon. Res. and Treat. Cent., Univ. N. C., Chapel Hill., NC, USA.

In the ten years since the cloning of the CF gene, our understanding of how the CF protein (CFTR) affects cellular physiology has substantially increased. However, a cure for the disease remains elusive. Gene therapy has been hampered by inefficient uptake of gene transfer vectors into relevant cells of the airway and lack of long-term expression. Barriers to efficient gene transfer and robust expression include: the lack of receptors or internalization proteins at the apical surface of the cells, the presence of the glycocalyx that prevents interaction of vectors with the cells by masking binding sites, the presence of the mucus layer that prevents vector from reaching the cell surface, and immune system responses that eliminate transfected cells. Current strategies to overcome these barriers will be discussed in the context of the airway. Aside from gene therapy, knowledge of how various mutations affect CFTR function has led to interest in development of therapies specific for individual mutations. For example, the most common CFTR mutation in many populations, ΔF508, leads to improper folding and degradation of the protein before it reaches the plasma membrane. Specific drugs treatments designed to increase the presence of the ΔF508 protein at the plasma membrane may prove valuable in patients who carry the ΔF508 allele. Mutations that lead to premature stop codons could potentially be corrected by drugs that would prevent premature protein truncation. Likewise, drugs that increase CFTR activity might be useful for missense mutations that generate CFTR that is properly processed and reaches the plasma membrane but that displays altered channel activity. The initiation of high throughput drug screening programs should aid in the development of therapies based upon CFTR mutations. Finally, as more is learned about the pathophysiology of CF disease, treatment options directed at proteins other than CFTR may prove to be valuable. For example, it may be possible to use amiloride-like drugs to decrease the activity of the epithelial sodium channel, which is known to be overactive in patients with CF, or to increase the activity of alternative chloride channels in an attempt to normalize the salt balance on the airway epithelium. The finding that mutations in Muc1, a transmembrane mucin molecule, can decrease the severity of intestinal disease in CF-deficient mice suggests that manipulation of mucin molecules interacting at the cell surface has potential benefit. The newly reported link between CFTR and arachidonic acid metabolism is also relevant to this discussion. In summary, although no cure for CF is presently available, the characterization of the CFTR gene and the effects of mutations on the biology of the cells has increased potential targets for therapies, and the future seems assuring.