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June 2, 2016

Luis Eduardo Bravo, M.D., MSc
Professor Emeritus of Pathology
Director, Population-based Cancer Registry of Cali
Universidad del Valle
Cali, Colombia

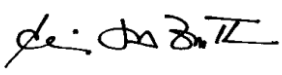
Dear Dr. Bravo:

It is my great privilege to review the seminal paper by Dr. Pelayo Correa on his proposed model of gastric cancer epidemiology which was published in 1975. I understand that my review will be one component of the consideration of his many achievements over a long and distinguished career in academia and science for the possible awarding of the Doctorate Honoris Causa by the Population-based Cancer Registry and the Universidad del Valle. That this paper by Correa was published in Lancet speaks to the importance of this work, as Lancet represents the very top tier of medical journals worldwide.

I will discuss the paper on a subsequent page from this cover letter, but I would like to say that I can think of no one more deserving of such an honor from the University and the Tumor Registry. Both institutions are near to his heart because of his strong affiliation of both. I have had the privilege to work for and with Dr. Correa since 1979. He is a remarkable thinker – creative and innovative. He has a unique capacity to synthesize scientific findings from different fields into a cohesive whole leading to one or more hypotheses which he subsequently explores until it is rejected, modified or accepted. That scientific exploration represents his stellar career from the early 1970s to this time. In addition to his research, throughout this career he has trained a generation of pathologists, epidemiologists, and other laboratory scientists as a generous and patient mentor. Each of us who has had the good fortune to learn from him will forever be in his debt.

I wish you success in your deliberations about this award. If I can provide any additional information please do not hesitate to contact me. I hope that Pelayo will indeed receive this auspicious award. I know that it would mean a great deal to him.

Sincerely,



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A MODEL FOR GASTRIC CANCER EPIDEMIOLOGY

Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M: *Lancet*, 1975; 2:58-60

In this 1975 paper Correa and colleagues hypothesized that the intestinal-type of gastric adenocarcinoma, the "epidemic form" of gastric cancer, arises as the end result of a cascade of events over many years. The observations supporting this hypothesis were the result of studies from Colombia, Japan, Scandinavia, and the United States. It was postulated that these events begin in early childhood and involve a lengthy pre-malignant process over 30 to 50 years. The progressive changes in the gastric mucosa begin with chronic gastritis, followed by multifocal atrophic gastritis and intestinal metaplasia as precursor conditions and lesions respectively.

While the model has been updated and expanded by Dr. Correa and others through an increasing knowledge base over time, the basic underlying model remains true as proposed. This paper has been cited in the scientific literature over 500 times and continues to be cited as the basis of much we know about gastric cancer, the second leading cause of cancer mortality worldwide. It was clear in the Correa model that the etiology of gastric cancer is multifactorial and that these factors result in changes to the gastric microenvironment. Mutations and cell transformations, epithelial changes from gastric to intestinal, detrimental and protective dietary factors, chronicity of exposures and resulting gastritis, and a key role for bacterial colonization of the stomach were all components of the model and they remain so today.

We now know that the bacterium Helicobacter pylori is the principal cause of gastric cancer. In 1975 H. pylori had not been discovered or named, although had been seen at the turn of the 20th century and dismissed by many as an artifact until Barry Marshall and Robin Warren found it in the stomach of a patient with chronic gastritis and gastric ulcer in 1982. This discovery was entirely consistent with the Correa model. Follow-up studies of this important link to gastric cancer causality were immediately undertaken by scientists worldwide, and Correa and colleagues were quick to pursue studies of H. pylori in the high gastric cancer-risk regions of Colombia in the Andes mountain area as well as comparative low risk regions in other parts of Colombia along the Pacific coast. Much has been learned over the years. The results of a chemoprevention trial of antioxidants vitamin C and beta carotene supplements and anti-Helicobacter triple therapy published in the Journal of the National Cancer Institute in 2000 demonstrated that each of the antioxidant supplements as well as the triple therapy significantly increased the regression of atrophy and intestinal metaplasia in patients receiving the treatment. The strongest and statistically significant increase in regression of the premalignant lesions of the stomach was demonstrated for study subjects who were cured of H. pylori infection and this occurred in 74% of the treated subjects. Sixteen years ago this trial provided experimental evidence of a potentially effective strategy to prevent gastric carcinoma.

The importance of infection in childhood was demonstrated by the Correa group who compared the age of acquisition of H. pylori infection two areas of Colombia with contrasting risks of gastric cancer reported in 2004. In the ensuing years, Correa's work and that of others has demonstrated the importance of strain characteristics of the key agent in gastric carcinogenesis, H. pylori. Likewise, the importance of host characteristics has been demonstrated by Correa et al. The genes linked to the immune response to chronic inflammation, such as the interleukins IL1 B and IL1 receptor antagonists, have been associated with gastric carcinogenesis. Several of these are tumor suppressors of gastric acid secretion which may facilitate bacterial colonization.

The environment, the host, the agent, all components of the pathology, epidemiology and chemistry of gastric carcinogenesis, were well captured by Correa's 1975 model and have guided years of research throughout the world and none more important than the research conducted in Colombia.