# A TRIBUTE TO PROFESSOR JOHN HO

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The organizers of this Fourth International Conference on EBV and Associated Diseases asked me to say a few words to introduce Professor John Ho to the participants of this meeting. This is not a duty for me, but a great and deep pleasure as we have travelled a long way together for more than 20 years.

John, do you remember the flight between Lyon and Paris, a Tuesday or Wednesday evening, in the fall of 1968? You were visiting Callam Muir and John Higginson at the IARC, the new International Research Institute created by Charles de Gaulle and the World Health Organization in Lyon, France, to boost cancer research and stimulate epidemiological studies at the international level. Was it chance, or had we, following Louis Pasteur's words "a prepared mind", when we sat next to each other in the Caravelle. It took only few minutes to realize that I was next to the world famous cancer emperor of Hong Kong: Dr. Ho, who was already deeply involved in studying and treating the Kwantung tumor.

1968! This was the time when the Epstein-Barr virus was just shown to be the cause of infectious mononucleosis, as discovered by Werner and Gertrude Henle with the involvement of a young post doctorate, Volker Diehl. This was the time when we were considering that Burkitt's lymphoma could represent a malignant infectious mononucleosis, and be caused by a severe primary infection by the Epstein-Barr virus. This was the time shortly after Lloyd Old's serendipitous observation that the sera from undifferentiated carcinoma of the nasopharynx, taken as controls of BL patients in the ENT department in Nairobi, Kenya, also exhibited high immunoprecipitating antibodies against the Epstein-Barr virus.

The flight between Lyon and Paris was only 45 minutes long, but this was sufficient for you and I to get acquainted and to share our respective passion: yours to discover the environmental cause of nasopharyngeal carcinoma and control it, mine to uncover the role of viruses in human tumors, specifically for NPC, with the hope to prevent them by antiviral intervention. Here we are 23 years after this initial flight, and after 20 years of collaboration and 28 collaborative publications. As is often the case in medical research, new knowledge raises new questions and the complexity of the interaction between genetic and environmental factors in the disease causation makes

progress slower than one wishes.

Between 1968 and 1978, there was a decade of golden years for the Epstein-Barr virus and the international network of scientists, involving yourself in the Far-East, Werner and Gertrude Henle in Philadelphia, George Klein in Stockholm, Harald zur Hausen in Germany and our group in Lyon. During this golden period, the association between the ubiquitous Epstein-Barr virus and this Chinese tumor was confirmed, and we showed with our colleagues in North Africa, that NPC was similar, if not identical, to the Chinese tumor in its histopathology and association with the Epstein-Barr virus. The usefulness of the EBV/NPC association for the benefit of the patients was carefully studied by yourself in collaboration with Werner Henle and with us.

Concerning EBV, let's be very frank, you were never too enthusiastic about the fact that an ubiquitous virus could represent the only critical agent for a tumor so geographically localized and which was, as you used to say ~ associated with poor living conditions, thus suggesting more an environmental chemical factor than a viral infection. But we know that transmission of viruses early in life is associated with poor hygiene.

In spite of the fact that we do not yet understand the mechanism by which the viral genes are involved in NPC development, still the humoral response to viral specific antigens is very instrumental to the control of the disease. Our eminent colleague and very good friend, Pro Xeng Yi from Beijing, was the first to implement large population surveys and screenings, using the IgA antibody test to detect this tumor at an early stage. You were very active in such an endeavour in Hong Kong. Through longitudinal studies, we observed that there was a direct relationship between the level of IgA antibody to VCA and EA, and the risk of developing nasopharyngeal carcinoma. Furthermore, we showed together with you, John, our colleagues at the Institute Gustave Roussy and our colleagues in Tunisia, that IgA antibodies to EA were critically instrumental to detect clinically silent relapse of the tumor, once the patients have been treated by radiotherapy and maintained disease-free for at least a year.

John, again, you were a pioneer in another field of NPC research, i.e. the role of environmental carcinogens in NPC causation. You were the first to accuse soft and hard preserved fish, shown to contain nitrosamines, as a possible cause of NPC. You were the first to show with Dolly Huang and others that rats fed with salted fish developed nasal carcinomas. You were the first to try to have an immediate impact on prevention of this disease, by requesting through the Hong Kong media, that young children not be fed with this Chinese delicacy, i.e. salted fish.

I must admit that I was late in accepting that chemical carcinogens could be so critical, but when I realized that the world over nasopharyngeal carcinoma did not have a

geographical distribution but an ethnic one, and when I saw that in the Guangxi Autonomous region, where the Han are at higher risk, some minority groups, living in the same geographical area, had a very low risk for NPC, I made a mental conversion and started to investigate possible chemical/viral interactions in NPC causation. Annie Hubert, in our group, proposed that certain preserved foods could play a role, and we have now come to the same conclusion that you presented nearly 20 years ago, namely that salted fish represents a critical risk factor, when consumed early in age.

You were also a pioneer for the last but not least factor involved in NPC causation, i.e. a genetic susceptibility to the disease. You were the first to suggest and evaluate the NPC risk within certain families, based on clinical questionnaires. You were the first to help and participate in an RLA-related case and control study, initiated by Malcom Simons in Singapore and by Nick Day and ourselves at the IARC, studies which progressively led to this recently published manuscript in Nature indicating that there most probably exists a disease susceptibility gene closely associated but independent from the RLA region. In parallel to that, Thomas Tursz, within the NPC study group at Institut Gustave Roussy in Villejuif, provided further evidence, in a case control study in Algeria, that indeed there was some RLA association with the disease. Does this genetic susceptibility control the immune response to the virus, or the metabolic response to the chemical carcinogens? The years ahead of us should unravel this fascinating puzzle involving an ubiquitous virus, specific chemical carcinogens linked to lifestyle, and genetic factors. Your many contributions to this disease has revolutionized research on NPC which will, hopefully, eventually lead to a cure. You richly deserve this honor being bestowed upon you by the EBV Association.

# EPIDEMIOLOGY OF NASOPHARYNGEAL CARCINOMA (NPC)

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I am deeply sensible of the honour conferred on me by the International Association of Epstein-Barr Virus and Associated Diseases by selecting me from among a host of deserving scientists and physicians for delivering this speech, and to be the recipient of an award for my past contributions to the epidemiological and clinical study of an important EBV-associated disease, nasopharyngeal carcinoma, a prevalent cancer in southern China and Southeast Asia. I was born and raised in Hong Kong, a part of southern China, and happen to be an oncologist. Consequently, I had the good fortune to be in the right place at the right time -- the right time because when I first started to study it in earnest in the late 1950's, the disease was very prevalent. . Actually, I first became interested in NPC while I was a medical student at the University of Hong Kong, where the Professor of Surgery at the time was Kenelm Digby, who was foremost among the early tillers of the obdurate ground of this cancer. During the Pacific War, I spent four years and nine months in the Chinese Army, moving from place to place without much contact with NPC patients, but the contact with villagers in different parts of southern China gave me valuable information about the way of life they led, especially during childhood, which was of use to me in subsequently studying the cause of NPC.

I first learned that there was a serological association between NPC and a herpesvirus, named Epstein-Barr virus, after its discoverers, from a paper by L.J. Old and his colleagues at the Sloan-Kettering Institute in New York in 1966. **In** 1968, while travelling to the International Agency for Research on Cancer (IARC) in Lyon, I happened to sit next to Dr. Guy de The of that Agency, on the plane. It was Dr. John Higginson, then the director of IARC, who provided the funds for the fruitful collaboration between the two of us, as mentioned in Guy's introductory speech. **In** 1969, I had the good fortune of meeting the two doyens of EBV immunology, Drs. Werner and Gertrude Henle, in Philadelphia, and the meeting resulted in a very productive collaboration in the study of the association between NPC and EBV. I sent the Henles coded serum samples without any information on the donors. I was amazed to find great accuracy of the serological tests used by them in sorting out patients with NPC from healthy subjects. Without their knowledge, I had also clinically staged the disease of each case of NPC according to my classification, which has been found to correlate very well

with prognosis. At our second meeting in Philadelphia, I asked them to see if there was any correlation between EBV titer and the stage. Next morning when we met again, he was very pleased to show me that there was a stepwise increase in the geometric mean antibody titres with advancing stages of the disease. Advancing stages means an increasing tumour cell popu1ation and hence, an increasing availability of viral antigens to stimulate the production of antibodies against them. That these viral antigens were produced by viral genetic material integrated within the tumour cells was shown in 1974 by our laboratory team, headed by D.P. Huang. We demonstrated the presence of the viral nuclear antigen (EBNA) in the nuclei of NPC cells. About the same time, working with my colleagues, H.C Kwan, who did all the serological examinations, M.H. Ng, of the Department of Microbiology of the University of Hong Kong, Daisy Saw, of the Department of Pathology of our hospital, W. H. Lau and other clinical colleagues in my former institute, the Queen Elizabeth Hospital, Kowloon, we demonstrated the usefulness of EBV serology in the diagnosis of NPC, and in the screening for early cases in a high risk population, the first-degree relatives of N"PC patients.

We have not put all our eggs in one basket. From studies in Singapore, it was found that Indians there had, as in the case of Chinese, a high incidence of EBV infection in childhood, but they had a very low incidence of NPC Consequently, either they have some unknown protective factors against a possible carcinogenic action of the virus, or, more likely, there are other co-factors involved in the carcinogenesis in Chinese but not in Indians. To narrow down the enormous number of possible co-factors for study, I first proceeded to find out whether they were inhalants or ingestants. The fact that Indians and Chinese living in the same general environment in Singapore have a marked difference in incidence of the NPC, and second generation Chinese in the U.S.A. still have a high incidence of the cancer, although lower than that of the first generation immigrants, made me suspect ingestants rather than inhalants to be the more likely culprit. As I was pondering over the matter, a junk manned by fisherfolks was serenely sailing past my view, as I was gazing at the distant sea through the window of my office at Queen Mary Hospital. An idea immediately flashed through my mind. The fisherfolks in Hong Kong traditionally live and work m their boats or junks, and cook in the open. They should have a lower incidence of the cancer if household carcinogenic inhalants were the culprit, as all workers thought at the time. I therefore studied and compared the incidence of NPC in the boat-dwelling fisherfolks and the land-dwelling population. To my big surprise, the fisherfolks had an incidence double that of the land-dwellers, the majority of whom lived in congested dwellings with poor ventilation. If ingestants were suspected, it was important to determine the critical period of life that the patients were exposed to them. I immediately studied the age-specific incidence curves of NPC. I found the curves for Chinese in Hong Kong and the U.S.A. have the same pattern - a sharp rise after the third

decade. Since the latency period, the period between the initiation of carcinogenesis and clinical manifestation, ranges in most internal solid cancers from 20 to over 30 years. I then looked for possible co-factors operating in early childhood life.

NPC has been afflicting southern Chinese with high frequency for at least three quarters of a century. It was formerly called "Canton" or "Guangzhou tumour". The living environment has chan6"ed significantly for many southern Chinese, especially those who had migrated overseas to Southeast Asia and the U.S.A., yet their NPC risk remained high. Consequently, it is unlikely that carcinogenic substances in the soil or drinking water or common foods consumed play an important causal role. We have, therefore, to study their traditional ingestants, because we inherit from our forbearers not only their genes, but frequently also their peculiar food culture. Salted fish is a traditional food item among southern Chinese, and happens to be one fed them, often as early as during the weaning period, cooked in rice porridge (conge e) to give it taste. Babies dislike insipid food. Known chemical carcinogens, known to be very potent in laboratory animals, have been detected in salted fish by our team collaborating with Terry A. Gough's team in London. When we fed young Wistar Albino rats salted fish, some of them developed carcinomas in the region of their nasal cavities. We cannot extrapolate this animal finding to man. The experiment only showed that consumed food could cause cancer in the respiratory tract, because digested food substances when absorbed into the blood stream can be conveyed to any part of the body. For a long time, workers tended to ignore this fact, and consequently, our findings were not initially all well received. It was not until Brian Henderson of the University of Southern California came to check our work and became convinced that he should join hands with us to examine my hypothesis that salted fish consumption at an early stage of life is an other important risk factor. Findings of subsequent collaborative epidemiological studies carried out with us in Hong Kong and with groups in Malaysia and China are strongly consistent with the hypothesis. Mimi C. Yu of Henderson's team must be given credit for her drive and untiring efforts that have made these studies possible. Henderson's team also confirmed the findings of our animal experiment. As other, more nutritious food, e.g. dairy products have become more readily available and cheaper, and salted fish more expensive, the traditional habit of Hong Kong Chinese feeding their children salted fish has been decreasing during the last four decades. It is tempting to suspect that the progressive decline in the age-adjusted incidence of NPC from 1974-1987 of 18% in males and 30% in females is related to the changing diet.

Most cancers are caused by a combination of factors. If only one of them, e.g. an environmental factor, is removed, the cancer will not develop. I have, as requested, given a short story of my involvement in the study of NPC, an EBV-associated disease. I said

earlier that I happened to have the good fortune to be in the right place at the right time. In fact, I was also in the right mix, working with the right people, which is even more important. Included among them were also Paul studied the age-specific incidence curves of NPC. I found the curves for Chinese in Hong Kong and the U.S.A. have the same pattern - a sharp rise after the third decade. Since the latency period, the period between the initiation of carcinogenesis and clinical manifestation, ranges in most internal solid cancers from 20 to over 30 years. I then looked for possible co-factors operating in early childhood life.

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