SCIENTIFIC CONTRIBUTIONS OF PROF. HAMAO UMEZAWA

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Professor Umezawa is recognized as a world leader in antibiotic therapeutic pharmacology. So remarkable are his achievements that one is reminded of Pasteur in the manner he sought to find practical and applicable agents, his drive to expand research in his field, and his probing approach to research. Professor Umezawa's discoveries of antimicrobial agents are beneficial to both medicine and patients. Of the more than 70 antimicrobial agents he discovered, kanamycin and kasugamycin are most notable. In the years following World War II when treatment for tuberculosis was streptomycin, there appeared resistant strains of the organism. In response to this, Prof. Umezawa discovered kanamycin in 1956 as an active antibiotic against TB as well as Gram-positive and Gram-negative organisms. He also determined the structure of kanamycin chemically and by X-ray crystal analysis. Thus when kanamycin resistant strains of organisms appeared in 1967, he was able to find that enzymes were involved in deactivating, and determined their structure. He determined that the enzymatic mechanism of resistance was to aminoglycosidic antibiotics and developed new kanamycin derivatives which showed therapeutic effect against resistant infection.

In 1962, he developed Kasugamycin to combat Piricularia oryzae, a fungus that was threatening to ruin Japanese rice fields. He again modified structures of old antibiotics and helped to shape the field of antibiotics.

Just as it was with Pasteur and his expansion of his field through to the development of the Pasteur Institute, so it was with Prof. Umezawa and the Institute of Microbial Chemistry. Through royalties brought in by the worldwide production of Prof. Umezawa's discovery, kanamycin, the Institute of Microbial Chemistry was established. Since his involvement in antibiotics, another department has been added to the University of Tokyo, the Department of Antibiotic studies. Through his activities, interest in antibiotics developed and along with it, wide-ranging

public support to ensure the continuity of such institutions.

Prof. Umezawa is also Pasteurian in the sense that he has a variety of scientific interests. His interests range from medicine, biochemistry, genetics, enzymology, microbiology to chemistry, and his ability to assimilate information from different disciplines is most impressive. So much so that scientists throughout the world consider him among the most important figures in the history of biomedical research. Therefore it is not surprising to find that his peers consider him a genius.

Prof. Umezawa is the pioneer of antitumor antibiotics study. In 1951, he initiated screening of antitumor antibiotics and in 1953 discovered novel bioactive microbial products that were active in inhibiting experimental animal tumor. He elucidated their structures and their structure-activity relationships which in turn allowed prediction of their active structures. Through these studies, he was able to create effective compounds for treatment of diseases. He studied structural relationships of antitumor antibiotics of complicated structures to their cytotoxic action against different types of cells, and established a new principle in the chemotherapy of certain types of tumor. As a result, he has found more than 30 antitumor antibiotics, and is presently still active in the field.

Of the many antitumor antibiotics, Hamao Umezawa's discovery of bleomycin is to be respected. It is the first successful finding of an effective agent in the treatment of a human solid tumor. Until then, there was no successful demonstration of any curative effect against cancer in general, nor was there any move to examine their effect on a specific type of tumor. Had it not been for Prof. Umezawa and his pursuit to extend antibiotic research to a more fruitful research area, the usefulness of the bleomycin might not have been fully realized and they would not have been developed into chemotherapeutic agents. Bleomycin was found to exhibit therapeutic effects on squamous cell carcinoma, Hodgkin's tumor and testis tumors. His studies on bleomycin and its clinical effect have stimulated the study of antitumor antibiotics aimed at finding effective cancer chemotherapy. Also with the successful application of the idea to produce derivatives of aminoglycosidic antibiotics useful in treatment of resistant infections and with the discovery from bleomycin studies which showed that enzymatic mechanisms of different cells are selective, it has been possible to apply these ideas to the establishment of chemotherapy of cancer and resistant infections. Hence, Prof. Umezawa's achievements concerning bleomycin and kanamycin can be said to be the greatest contribution to

date in the therapy of cancer and resistant infections.

In 1966, Prof. Umezawa initiated the study of small molecular enzyme inhibitors produced by microorganisms, as reviewed in his book "Enzyme Inhibitors of Microbial Origin" (University of Tokyo Press). He initiated the screening of microbial products which inhibit proteases and demonstrated the existence of enzyme inhibitors of small molecular nature in culture filtrates. Enzyme inhibitors are valuable tools in the analyses of biological functions and disease processes. Here again Prof. Umezawa's protease inhibitors (leupeptin, antipain, elastatinal, pepstatin, phosphoramidon and bestatin) have been widely used in biological and medical studies all over the world.

He also developed an ingenious screening method to find compounds which affect immune responses. He reasoned that inhibitors of enzymes on the surface of cells should bind to the surface of cells involved in immune reactions. Thus, by looking for these inhibitors of enzymes on the cell surface, he discovered small molecular microbial products which would enhance or suppress immune responses.

Prof. Umezawa continued to follow up on the chemical structures of antibiotics and enzyme inhibitors. He perceived a significant meaning from the evidence that compounds of widely varying structure and various types of bioactivity were produced by microorganisms, and noticed that each contains a characteristic chemical structural part or a biosynthetic intermediate common to a group of secondary metabolites. This led him to propose a principle for genetics and biosynthesis of microbial secondary metabolites. He first noticed a possible involvement of a plasmid in the biosynthesis of some antibiotics.

Professor Umezawa's ever persistent pursuit of what he calls "new problem areas or old ones that have been ignored or avoided as being too troublesome" have brought him pioneering achievements in antitumor antibiotics and exhibition of therapeutic effect on certain types of tumors and enzyme inhibitors, elucidation of the structure-activity relationships or aminoglycosidic antibiotics to inhibit resistant infections, development of useful compounds with novel bioactivities, revelation of plasmid involvement in biosynthesis, discovery of novel bioactive microbial secondary metabolites and determination of their structures.

They are findings of major historical significance.

They are the findings of a man who says "research is my habit" and thrives on it. Professor Umezawa is indeed the "most productive" creator of new medicines, as quoted by a leader of research in the United States.