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Società Svizzera di Microbiologia *Rendiconti della 44a sessione annuale*

Swiss Society of Microbiology *Reports of the 44th annual meeting*

Geneva, 11–13 April 1985

The Society Prize 1985

The Society Prize has been allocated to Dr Jon Duri Tratschin, Institute for Hygiene and Medical Microbiology, University of Bern, CH-3000 Bern, Switzerland

Main Lectures

Prof. Luc Montagnier, Institut Pasteur, Paris, France
Prof. J. E. Davies, Biogen SA, Geneva, Switzerland
Dr H. Mahler, Director-General WHO, Geneva, Switzerland
Prof. J. Skehel, National Institute for Medical Research, London, GB

Main Lectures

Role of lymphadenopathy associated virus (LAV) in the pathogenesis of the acquired immunodeficiency syndrome (AIDS)

L. Montagnier
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Epidemiological data collected in 1981 and 1982 suggested that AIDS was transmitted by an infectious agent present in blood and sperm. AIDS cases observed in hemophiliacs receiving commercial filtered preparations of factors 8 and 9 indicated that this infectious agent could be a virus. Indeed a new type of human retrovirus, LAV, first isolated from patients with persistent lymphodenopathy and thereafter from patients with frank AIDS, is now considered as the primary etiologic agent of the disease.

In the absence of direct reproduction of the disease by inoculation of the virus into animals, indirect evidence strongly suggests a causal relationship:

1) Frequent isolation of the same type of virus from all groups of patients with AIDS or AIDS-related complex (homosexuals with multiple partners, hemophiliacs, i.v. drug users, Haïtians, Africans) and unfrequent isolation from patients with other diseases or from healthy individuals of the general population.

2) Documented cases of transmission of the virus via blood transfusion.

3) Tropism of the virus for the $T4^+$ subset of lymphocytes with induction of cytopathic effect.

4) Prevalence of antibodies against viral proteins in AIDS and ARC patients and also in asymptomatic carriers of the virus belonging to the high risk groups.

5) Confirmation of these data by several laboratories.

Acute LAV infection is most frequently inapparent or may eventually result in signs described as the AIDS-related complex. The occurrence of AIDS is relatively rare and often requires a long incubation period, which allows the interplay of cofactors, such as repeated antigenic stimulation and a terrain of immune depression. Analogy with the slow retroviruses (lentiviruses) is suggested by some similar aspects of the pathogenicity (neurological signs) and the structure of the AIDS retrovirus itself. LAV is clearly the prototype of a new group of human retroviruses, not related to human leukemia viruses (HTLV I and II).

Biotechnology 1985: from proteins to small molecules

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Biotechnology is one of the oldest industries and certainly represents one of the first applications of science to the benefit of mankind.

There are essentially three areas of technical development which have led to the explosion of gene technology approaches to problems of biotechnology:

1) Gene transfer
2) Gene expression
3) Gene manipulation

Standard cloning procedures have been refined to the extent where any activity, protein or coding sequence may be detected. We are in a position to find gene products that were unsuspected and that may have novel physiological activity by using the network of routes available in gene cloning methodology.

A large number of mammalian proteins have been cloned and expressed and already the pharmaceutical applications of this genetic engineering approach have become apparent. The production of mammalian proteins is a relatively 'easy' goal for recombinant DNA; it is only necessary to clone and express single genes and inter-

actions with other gene products or with the host are usually not important. However, there are other organisms and products that are worthy targets for this novel scientific approach and in fact, in the case of small molecules, the types of problems to be solved are very different from those encountered in the cloning and expression of single genes. The problem is much more difficult, but also worthwhile. Are not the majority of pharmaceuticals, used at the moment, classed as small molecules? Virtually none are proteins! Therefore it is natural that recombinant DNA should want to turn to engineering of microorganisms. In addition, the possibilities of engineering higher yields and altered molecules of pharmacologically active chemicals such as the alkaloids provides a strong impetus for studies of plant biosynthesis.

The problems lie not in the fact that small molecules are involved but that one has to control multiple enzymatic reactions. Small molecules, whether they be the products of primary or secondary metabolism, are made by complex biosynthetic pathways which possess, in many cases, delicately balanced regulatory and control mechanisms. For example the genetic engineering approach to increasing antibiotic production is an obvious application, but not an easy one. The producing hosts are often not well studied or characterized biochemically, the biosynthesis of the small molecule (and its regulation) is not well known, and appropriate host/vector systems are not available. This creates a situation in which, to augment or to modify a given antibiotic, a complete analysis of the producing organism must be completed and suitable vectors for this organism constructed. Substantial progress has been made and several approaches to antibiotic yield improvement using recombinant DNA techniques have shown promise. One important finding is that many of the biosynthetic genes for antibiotics may be clustered on the chromosome and therefore easy to pluck out and manipulate. In addition, antibiotic resistance genes are found within these clusters, providing convenient probes to identify the biosynthetic pathway genes.

Genetic engineering methods are novel, exciting and undoubtedly useful. To be effective in a broad range of applications will require a better knowledge of the physiology and biochemistry of the organisms that need to be manipulated, and of the systems to which recombinant DNA products will be applied.

Of microbes and man

H. Mahler
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Infectious disease, which preceded the emergence of mankind, will last as long as humanity itself and will surely remain one of the fundamental parameters and determinants of human history, but not with the same interaction/impact worldwide. In the early ages, life in small family clusters was not conducive to wide-spread infection. When these clusters expanded, microbes could spread further and cause illness which became more feared as they would frequently appear in several members of the tribe at one and the same time. The wrath of the gods appeared to be a reasonable explanation to this phenomenon, and the priest/healer was chosen to act as the intermediary to appease the gods and prevent disease.

The industrial revolution brought people closer together in urban conglomerations thus increasing the opportunities for infections to spread. However, during the second half of the 19th century mortality declined almost entirely due to a decrease in deaths from infectious disease, especially tuberculosis, typhus, typhoid and related fevers, scarlet fever, cholera, dysentery and diarrhoea, and smallpox. The most important factors responsible for this decline in mortality were firstly, a rising standard of living, of which the most significant feature was probably improved diet, secondly, improved hygiene, and thirdly, a favorable trend in the relationship between infectious agent and human host.

By the turn of the century 'Man the Technician' was well on the way to 'conquering' microbes in the industrialized countries, just as he was becoming aware of their existence. It was at that time that the great discoveries of Pasteur and Koch were claiming worldwide recognition. Twentieth century data show that the continued decline in the death rate after 1900 in industrialized countries was also due mainly to a decrease in deaths from infectious disease such as measles, scarlet fever, whooping cough, smallpox and diphtheria, as well as tuberculosis, typhoid, paratyphoid, dysentry, influenza and syphilis. Lower mortality was also noted from groups of communicable diseases such as diarrhoea and enteritis, convulsions in infancy (usually associated with infection) and the respiratory infections – bronchitis and pneumonia.

In 1935 the first real antimicrobial drug the sulphonamide was introduced by Paul Ehrlich. The key discovery was that certain dyes would be taken up by, and would kill, parasites and bacteria, while leaving patients' tissues alone. In short, Ehrlich introduced the notion of drug specificity, of the 'magic bullet'.

The attack on microbes did not become a worldwide reality until after the Second World War when antimicrobial agents such as penicillin and sulphonamides became widely available. In addition, vaccines against specific diseases were being developed at a fast rate. The conquest of infectious diseases seemed to be near in the 1950s, and an aura of elated optimism reigned. However since then, morbidity rates of infection have not decreased significantly and in some cases have actually increased. In addition, changes in the structure of society and in social behavior as well as changes in medical practice (especially the extensive use of blood and blood products) have favored the spread of 'new' diseases in the community such as Legionnaire's disease and AIDS. The indiscriminate use of antibiotics has meantime favored the selection of antibiotic-resistant organisms.

Only a minority of the world's population have benefited from the development engendered by the industrial revolution. In the developing world, communicable diseases, complicated by malnutrition and other adverse socioeconomic factors, continue to contribute greatly to the unacceptably high levels of morbidity, mortality and disability particularly in the under-five age group. It is estimated that five million deaths occur annually from diseases which can be prevented by vaccines available today, and that another five million people are being crippled,