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Bacterial plasmids are circular double-stranded DNA molecules that are physi cally separate from the bacterial chromosome. They are replicated and stably inherited in the extrachromosomal (autonomous) state. The plasmids of entero bacteria can be divided into two distinct groups according to their size: (i) small plasmids with MW of less than 10 Mdal, and (ii) large plasmids with MW ranging from 50-100 Mdal. These two groups differ strikingly in their copy numbers per cell (multiplicity). Whereas most small plasmids are multicopy plasmids (20-100 copies per cell), large plasmids are normally present at a multiplicity similar to the number of chromosomal genome equivalents (oligo copy plasmids). Furthermore, large plasmids can promote the transfer of DNA by conjugation and are therefore classified as conjugative plasmids. Since this property depends on the presence of the tra operon, a 15-20 Mdal segment of DNA (Helmuth and Achtman, 1975), small plasmids are necessarily nonconju gative. Because of their inability to mediate DNA transfer, small plasmids have often been designated as "nontransmissible. " This is clearly a misnomer since nonconjugative plasmids can in general be mobilized for conjugal transfer by a conjugative plasmid present in the same cell. Plasmids can further be classified with respect to their ability to continue replication in the absence of de novo protein synthesis (stable replication).

This volume has gathered some of the experts in the field to review aspects of our understanding of CMV and to offer perspectives of the current problems associated with CMV. The editors and authors hope that the chapters will lead to a better understanding of the virus that will assist in the development of new and unique antivirals, a protective vaccine, and a full understanding of CMV's involvement in human disease.

In recent years, plants have been increasingly explored for production of biomedicines and vaccine components. The two main advantages of plant systems are low cost and a greater potential for scalability as compared to microbial or animal systems. An additional advantage from the public health point of view is high safety compared to animal systems, which is important for vaccine production: there are no known plant pathogens capable of replicating in animals, and in humans in particular. A particular antigen or a protein has to be expressed in a plant using one of many available platforms; this antigen/protein subsequently needs to be purified or processed, and later formulated into a vaccine or a therapeutic; these need to be delivered to a human or animal body via an appropriate route. Naturally, all these vaccines and therapeutics must be subjected to regulatory approvals prior to their use. Thus, the challenge is to adapt plant-based platforms for production of cost-efficient biomedicals that can be approved by FDA for use as vaccine components or therapeutics which will be competitive against existing vaccines and drugs. This volume attempts to address the entire spectrum of challenges facing the nascent field of plant-based biomedicals, from the selection of an appropriate production platform to specific methods of downstream processing and regulatory approval issues.

The term humanized mouse in this text refers to a mouse in which human tissues and cells have been transplanted and show the same biological function as they do in the human body. That is, the physiological properties and functions of tra- planted human tissues and cells can be analyzed in the mouse instead of using a living human body. It should therefore be possible to study the pathophysiology and treatment of human diseases in mice with good reproducibility. Thus, the hum- ized mouse can be used as a potent tool in both basic and clinical research in the future. The development of appropriate immunodeficient mice has been indispensable in the creation of the humanized mouse, which has been achieved through many years of efforts by several laboratories. The first stage on the road to the

humanized mouse was the report on nude mice by Isaacson and Cattanach in 1962. Thereafter, nude mice were studied in detail by Falanagan and, in 1968, Pantelouris found that these mice have no thymus gland, which suggested that the mice lack transplan- tion immunity against xenografts such as human hematopoietic stem cells. At the Nude Mouse Workshops (organized by Regard, Povlsen, Nomura and colleagues) that were held nine times between 1972 and 1997, the possibility of creating a humanized mouse using nude mice was extensively examined. The results, however, showed that certain human cancers can be engrafted in nude mice, but unfortunately engraftment of normal human tissue was almost impossible.

Continuous genetic variation and selection of virus subpopulations in the course of RNA virus replications are intimately related to viral disease mechanisms. The central topics of this volume are the origins of the quasispecies concept, and the implications of quasispecies dynamics for viral populations.

This volume covers all aspects of infection by pathogenic Leptospira species, the causative agents of the world's most widespread zoonosis. Topics include aspects of human and animal leptospirosis as well as detailed analyses of our current knowledge of leptospiral structure and physiology, epidemiology, pathogenesis, genomics, immunity and vaccines. Updates are presented on leptospiral systematics, identification and diagnostics, as well as practical information on culture of Leptospira. Contact information is also provided for Leptospira reference centers. All chapters were written by experts in the field, providing an invaluable reference source for scientists, veterinarians, clinicians and all others with an interest in leptospirosis.

This volume reviews the current research focused on the functional importance of unfolded protein response (UPR) signaling in the context of health and disease. The chapters present cutting-edge work describing the diverse functions of UPR signaling critical for regulating cellular and organismal physiology under physiologic and pathologic conditions. Written by internationally respected scientists, this volume is designed to provide a broad view of the diverse functional importance of UPR, and as such appeals to clinicians and academic researchers alike.

Workshops on the mechanisms of B cell neoplasia have been organized alternatively in Bethesda and Basel since 1983. Prog ress in our understanding of the development and responses of B lymphocytes is presented and discussed with the aim and hope to understand what might go wrong when B lymphocytes are transformed into malignant cells. Such knowledge might lead to better diagnosis, prevention and even cure of these terri ble diseases. The presentations at the Bethesda workshops are published as papers in volumes of Current Topics in Microbiol ogy and Immunology, while the presentations and discussions in Basel were transcribed and published in Editions Roche. For the first time, a Basel workshop (held 4th-6th October 1998) that has been recorded and, in part, transcribed is being published as papers and discussions within Current Topics. This volume is the latest of a long series which documents the excitements of ground-breaking discoveries as well as the frustrations of our inability to fully understand the mechanisms leading to B cell neoplasia. The papers at the workshop are presented when possible in the sequence in which they were given. However, to facilitate the organization and reading of the book and to highlight gen eral topics and themes, the papers are organized into five sec tions: I B Cell and Plasma Cell Development II Chemokines and Chemokine Receptors III

Chromosomal Translocations, DNA Rearrangements and Somatic Hypermutations IV Biology of Lymphomagenesis, B-CLL, Autoimmunity V Myeloma, Plasmacytomas and Related Subjects.

The processes involved in herpesvirus replication, latency, and oncogenic transformation, have, in general, been rather poorly defined. A primary reason for this is the size and complexity of the herpesvirus genome. Undoubtedly, a better understanding of the functions of the viral genome in infected and transformed cells will be achieved through studies with temperature-sensitive (ts) mutants of herpesviruses since, theoretically, any essential gene function can be affected by mutants of this type. A. The Herpesviruses A consideration of the genetic analysis of members of the herpesvirus group necessitates a description, albeit brief, of the properties of the group and, most importantly, of their genetic material. The herpesviruses comprise a group of relatively large (100-150 nm), enveloped viruses. The envelope surrounds an icosahedral capsid enclosing a core which contains double stranded DNA (ROIZMAN, 1969). The group is thus defined on the basis of a common virion morphology. In addition to a common structure, members of the group share a number of biological properties such as a similar replicative cycle, the ability to cause latent and chronic infections, and the ability to induce antigenic modifications of infected cell membranes. Several herpes viruses have been associated recently with malignancies in man and animals (KLEIN, 1972). Herpesviruses are ubiquitous and have been described in over 30 different species (HUNT and MELENDEZ, 1969; WILDY, 1971; FARLEY et aI. , 1972; KAZAMA and SCHORNSTEIN, 1972; NAHMIAS et aI. , 1972; ROlZMAN et aI. , 1973). Their widespread occurrence in nature suggests a common ancestor.

Throughout the biological world, bacteria thrive predominantly in surface-attached, matrix-enclosed, multicellular communities or biofilms, as opposed to isolated planktonic cells. This choice of lifestyle is not trivial, as it involves major shifts in the use of genetic information and cellular energy, and has profound consequences for bacterial physiology and survival. Growth within a biofilm can thwart immune function and antibiotic therapy and thereby complicate the treatment of infectious diseases, especially chronic and foreign device-associated infections. Modern studies of many important biofilms have advanced well beyond the descriptive stage, and have begun to provide molecular details of the structural, biochemical, and genetic processes that drive biofilm formation and its dispersion. There is much diversity in the details of biofilm development among various species, but there are also commonalities. In most species, environmental and nutritional conditions greatly influence biofilm development. Similar kinds of adhesive molecules often promote biofilm formation in diverse species. Signaling and regulatory processes that drive biofilm development are often conserved, especially among related bacteria. Knowledge of such processes holds great promise for efforts to control biofilm growth and combat biofilm-associated infections. This volume focuses on the biology of biofilms that affect human disease,

although it is by no means comprehensive. It opens with chapters that provide the reader with current perspectives on biofilm development, physiology, environmental, and regulatory effects, the role of quorum sensing, and resistance/phenotypic persistence to antimicrobial agents during biofilm growth.

Current Topics in Microbiology and ImmunologySpringerCurrent Topics in Microbiology and ImmunologyErgebnisse der Mikrobiologie und ImmunitätsforschungSpringer Science & Business MediaCurrent Topics in Microbiology and Immunology / Ergebnisse der Mikrobiologie und ImmunitätsforschungSpringerMechanisms of B Cell Neoplasia 1998Proceedings of the Workshop held at the Basel Institute for Immunology 4th–6th October 1998Springer

This volume brings together contributions from experts in the field of Pasteurella research. Its covers areas such as comparative genomics, pathogenic mechanisms, bacterial proteomics, as well as a detailed description and analysis of PMT and its interaction with host tissues, cells, immune system, and signalling pathways.

The expression of many bacterial genes adapts itself in an almost in stantaneous and reversible way to specific environmental changes. More specifically, the concentration of a number of metabolites, a function of the amounts of enzymes involved in their synthesis or degradation, in turn retroacts on the rate of synthesis of these enzymes. The genetic bases for this regulation were established by JACOB and MONOD (1961). These authors also showed how the known elements of these regulatory mechanisms could be connected into a wide variety of circuits endowed with any desired degree of stability, in order to account for essentially irreversible processes like differentiation (MONOD and JACOB, 1961). The general principles used by JACOB and MONOD in their study of negative regulation were extended to positive regulation by ENGLESBERG et al. (1965). An independent approach permitted the discovery of positive controls in temperate bacteriophages (see below, III). Each control operation is mediated by a pair of complementary genetic elements (hereafter called "control cell"): a control gene which produces a l control (or regulator) protein and a control site which is the target for the regulator protein. Negative control means that the control protein (repressor) prevents gene expression. One deals with positive control when the control protein (activator) is necessary for this expression. It has become apparent that, as initially postulated by JACOB and MONOD, control of gene expression operates, at least to a large extent, at the transcriptional level.

This volume of Current Topics in Microbiology and Immunology covers diverse topics related to intradermal immunization. The chapters highlight the effectiveness of intradermal immunization in experimental animal models or in clinical practice, all supporting the view that intradermal immunization is at least as good as other immunization routes. Keeping in mind that current vaccines are not specially designed for intradermal immunization, but show comparable efficiency even at reduced dosages, this underlines the great potential for the skin as a vaccination site. Hopefully, the

overview in this volume will encourage vaccine designers to focus on this promising immunization route, and in addition, to inspire them to develop vaccines that are especially optimized for intradermal immunization.

Several discoveries are noteworthy for allowing us to probe the recesses of the virus?? infected cell and to search for cryptic viral genomes which might provide clues in our studies of cancer etiology or developmental biology. One of the most notable was the dis?? covery of reverse transcriptase. This marked a momentous occasion in the history of molecular biology. Not only did it provide insight into the mechanism of persistence of retroviruses but it also provided us with an enzyme that could synthesize a DNA copy of any RNA. This DNA copy could then be used as a hybridization reagent to search for both complementary DNA and viral-specific RNA. Thus one could follow the course of any viral infection or probe in tumor cells for hidden viral genomes. Second, a great deal of credit must be given to the geneticists who isolated the various deletion mutants in the 'avian retrovirus system and thus provided us with the frrst means of isolating gene-spe?? cific probes. Finally, the laboratories which have mapped the genome have provided us with the framework in which to ask very specific questions with our gene-specific probes. Recently, numerous excellent reviews concerning various aspects of the retroviruses have appeared. In this review I shall not even attempt to present a comprehensive review of retroviruses.

Measles, also called the greatest killer of children in history, still annually affects about 50 million individuals and causes close to a million deaths primarily in developing countries. Before the advent of measles vaccine some 30 years ago, these figures were roughly three times higher. Attenuated measles virus (MV) strains, all quite closely related to the original Edmonston isolate, have a very good record as a safe and highly efficacious vaccine and have brought down the measles toll in industrialized countries to almost negligible levels. However, recent outbreaks in the USA and Europe have again brought the measles problem to public attention. Sadly enough, these outbreaks were more instrumental in inducing activities to drastically reduce and hopefully finally eradicate measles than were the ten thousand times higher number of victims in developing countries. To reach this goal, as detailed in this volume, apparently it is not enough to of the existing vaccine as was the rigorously enforce use case with smallpox eradication: the intricacies of measles disease phenomena, in particular the generalized immune suppression which favors secondary infections, require more basic knowledge of the virus-host interactions and probably the development of new vaccines for special applications such as first immunizations of very young infants in developing countries.

Hepatitis delta virus (HDV), which causes severe acute and chronic liver disease, was discovered nearly 30 years ago following the detection of a novel antigen-antibody system in hepatitis B virus carriers. HDV has continued to surprise and fascinate medical science ever since. This volume reviews recent developments in HDV research, from molecular virology to genetics to experimental investigation of new therapeutic and vaccine candidates.

Scientific research on dengue has a long and rich history. The literature has been touched by famous names in medicine- Benjamin Rush, Walter Reed, and Albert Sabin, to name a very few- and has been fertile ground for medical historians . The advances made in those early investigations are all the more remarkable for the limited tools available at the time. The demonstration of a viral etiology for dengue fever, the recognition of mosquitoes as the vector for transmission to humans, and the existence of multiple viral variants (serotypes) with only partial cross-protection were all accomplished prior to the ability to culture and characterize the etiologic agent. Research on dengue in this period was typically driven by circumstances. Epidemics of dengue created public health crises, although these were relatively short-lived in any one location, as the population of susceptible individuals quickly shrank. Military considerations became as a major driving force for research.

With the introduction of large numbers of non-immune individuals into endemic areas, dengue could cripple military readiness, taking more soldiers out of action than hostile fire. Dengue and dengue hemorrhagic fever, which assumed pandemic proportions during the latter half of the last century, have shown no indication of slowing their growth during this first decade of the twenty-first century. Challenges remain in understanding the basic mechanisms of viral replication and disease pathogenesis, in clinical management of patients, and in control of dengue viral transmission. Nevertheless, new tools and insights have led to major recent scientific advances. As the first candidate vaccines enter large-scale efficacy trials, there is reason to hope that we may soon "turn the corner" on this disease.

Phenomena as diverse as tuberculin sensitivity, delayed sensitivity to soluble proteins other than tuberculin, contact allergy, homograft rejection, experimental autoallergies, and the response to many microorganisms, have been classified as members of the class of immune reactions known as delayed or cellular hypersensitivity. Similarities in time course, histology, and absence of detectable circulating immunoglobulins characterize these cell-mediated immune reactions in vivo. The state of delayed or cellular hypersensitivity can be transferred from one animal to another by means of sensitized living lymphoid cells (CHASE, 1945; LANDSTEINER and CHASE, 1942; MITCHISON, 1954). The responsible cell has been described by GOWANS (1965) as a small lymphocyte. Passive transfer has also been achieved in the human with extracts of sensitized cells (LAWRENCE, 1959). The in vivo characteristic of delayed hypersensitivity from which the class derives its name is the delayed skin reaction. When an antigen is injected intradermally into a previously immunized animal, the typical delayed reaction begins to appear after 4 hours, reaches a peak at 24 hours, and fades after 48 hours. It is grossly characterized by induration, erythyma, and occasionally necrosis. The histology of the delayed reaction has been studied by numerous investigators (COHEN et al. , 1967; GELL and HINDE, 1951; KOSUNEN, 1966; KOSUNEN et al. , 1963; MCCLUSKEY et al. , 1963; WAKSMAN, 1960; WAKSMAN, 1962). Initially dilatation of the capillaries with exudation of fluid and cells occurs.

This volume focuses on antibiotics research, a field of topical significance for human health due to the worrying increase of nosocomial infections caused by multi-resistant bacteria. It covers several basic aspects, such as the evolution of antibiotic resistance and the influence of antibiotics on the gut microbiota, and addresses the search for novel pathogenicity blockers as well as historical aspects of antibiotics. Further topics include applied aspects, such as drug discovery based on biodiversity and genome mining, optimization of lead structures by medicinal chemistry, total synthesis and drug delivery technologies. Moreover, the development of vaccines as a valid alternative therapeutic approach is outlined, while the importance of epidemiological studies on important bacterial pathogens, the problems arising from the excessive use of antibiotics in animal breeding, and the development of innovative technologies for diagnosing the “bad bugs” are discussed in detail. Accordingly, the book will appeal to researchers and clinicians alike.

In the last few years the major effect that RNAi has had in invertebrate systems is beginning to take hold in mammalian systems through both single gene knockdown experiments and genome-scale screens. In the next decade, there will no doubt be both notable successes and failures as we attempt to apply this genetic tool to various biological problems. Through the introduction of RNAi, mammalian systems have finally gained admittance to the pantheon of model genetic systems.

Retroviruses have been of great importance to biomedical science for the past half century. Initially, studies on oncogenic animal retroviruses provided important insights into molecular processes in carcinogenesis – most notably the existence and mechanisms of action of oncogenes and proto-oncogenes. Moreover, several human diseases are caused by

retroviruses, including AIDS, adult T-cell leukemia and the neurological disease HAM/TSP. The topic of this volume is a relatively unknown animal retrovirus, jaagsiekte sheep retrovirus, the causative agent of transmissible lung cancer in sheep –ovine pulmonary adenocarcinoma. The disease was first documented in South Africa in the 1800s, it has a wide geographical distribution, and it is of economic importance in high endemic regions. However, until very recently the nature of the etiologic agent was unclear, and relatively few laboratories actively studied the disease.

Expression of an immune response is the net result of complex synergis tic and antagonistic activities performed by a variety of cell types. It includes macrophages, T and B populations which may interact in performance of a response, and suppressor cells interfering with it. Accordingly, a lack of res ponse may not necessarily indicate absence of immunocompetent cells, but rather nonexpression of competence. Thus, one should consider two possible situations, which are by no means mutually exclusive, to account for immuno logic unresponsiveness: (a) one or more of the cell populations composing the synergistic unit is absent or immature, and (b) an antagonistic unit which interferes with the response is dominating. In view of this, an approach to development of immune reactivity necessitates parallel surveys of development of cells with the potential to perform, as well as of cells which can suppress the response. Classification of the various cell types has been based so far on their phenotypic properties (e. g. , membrane antigen markers, cell receptors, pro duction and secretion of immunoglobulins, etc.). Genotypically, T and B cells may represent either separate, independent cell lines, or different stages of development within the same cell lineage.

Hepatitis C virus (HCV), a major causative agent of chronic liver disease, is spread throughout the world and around 170 million people are persistently infected. In this volume, world-leading experts in the field of HCV research have compiled the most recent scientific advances to provide a comprehensive and very timely overview of the various facets of HCV. The book starts with a discussion of the possible origin of HCV and its spread among the human population. The focus of the subsequent chapters is on available cell culture and in vivo models before shifting to the molecular and cellular principles underlying the viral replication cycle. These chapters are complemented by insightful descriptions of the innate and adaptive immune responses to HCV as well as the virus-associated pathogenesis. Finally, the development of antiviral therapies, which is closely linked with progress in basic research, and the implementation of those therapies into present and future daily clinical practice are highlighted.

This comprehensive, interdisciplinary book covers different aspects of relevant human pathogens and commensals. The ongoing development of (meta-)genomic, transcriptomic, proteomic and bioinformatic analyses of pathogenic and commensal microorganisms and their host interaction provides a comprehensive introduction to the microbiological analysis of host-microbe interplay and its consequences for infection or commensalism.

Clostridium difficile has been recognized as the cause of a broad spectrum of enteric disease ranging from mild antibiotic-associated diarrhea to pseudomembranous colitis. This volume gives new insights into the microbiology, diagnostics and epidemiology of Clostridium difficile and describes recent strategies in treatment of diseases caused by this agent. Main parts of the volume are devoted to Clostridium difficile toxins A and B which are the major virulence factors. The molecular biology, biochemistry, pharmacology and cell biology of these toxins which are the prototypes of a new family of large clostridial cytotoxins is described in great detail. Clostridium difficile toxins act as glucosyltransferases to inactivate small GTP-binding proteins of the Rho family which are involved in regulation of the actin cytoskeleton, cell adhesion and various signaling processes.

This volume discusses the interactions between viruses and their host cells, and explores the roles of host and viral genes and non-coding RNAs in the virus replication cycle. During infection, viruses express a variety of genes, encoding proteins and RNAs that serve to subjugate the cell – by redirecting cellular processes to support viral replication and, at the same time, by mitigating the cellular response to infection. In this book, experts discuss these interactions in depth, and elaborate on our current understanding of virus-cell interactions for a diverse range of viruses, including positive and negative sense RNA viruses, DNA viruses, and a vector-borne virus. The roles of non-coding RNAs are also discussed. While each class of viruses has distinct replication requirements, this volume reveals unique features and commonalities in viral replication cycles. Accordingly, it represents a valuable source of information for researchers and clinicians alike.

The external signals that control cellular behavior are chanelled through cell surface receptors, that in turn regulate cytoplasmic signaling pathways. Work over the last ten years has indicated that the activation of these intra- cellular signaling pathways depends on a series of protein-protein and protein-phospholipid interactions mediated by modular polypeptide domains. Through their association with specific peptide motifs, these protein modules define a recognition code through which many aspects of cellular function are controlled. The articles in this book describe the varied features of these domains, and outline the structural, biochemical and genetic evidence that demonstrates their importance in co-ordinating cellular responses to external cues.

This volume contains seven chapters, based on papers presented at a Symposium on Insect Viruses, held in conjunction with the 67th Annual Meeting of the American Society for Microbiology in New York, N. Y. , on 30 April-4 May, 1967. The Symposium was organized to bring together outstanding workers interested in various areas of insect virology, and allow an opportunity for a discussion of problems, approaches, and methods that would lead to further progress in basic and applied research. One of the princi pal reasons for holding the Symposium at this time was the feeling that the divergent areas of research, up to now studied separately by entomologists, medical and public health workers, geneticists, and plant pathologists, would be brought together, crossing the artificial borders and finding new, exciting and inspiring vistas. Insect viruses provide a rare opportunity to get acquainted with the work and methods of investigators in such related

and yet distant fields. Following the symposium, a decision was made to publish the papers in a single volume, extending the contents to provide a complete and scholarly review of each subject. Since viruses affecting insects have received little attention until recent years, it was felt that a fully documented presentation of diverse areas of insect virology merited publication. The invited authors, all recognized authorities in their respective fields, prepared their contri butions in such a way that each is a concise unit.

This book offers a comprehensive review of basic and clinical research on Varicella-zoster Virus, the only human herpesvirus for which vaccines to prevent both primary and recurrent infection are approved.

This edited volume explores Campylobacter species, which are some of the most important foodborne pathogens. Above all, contaminated poultry meat can cause human gastroenteritis in both developed and developing countries. The respective contributions reveal how these infections can also increase the risk of generalized paralytic diseases such as Guillain-Barré syndrome, Miller-Fisher syndrome, and Chinese paralytic syndrome. Due to their influence on the nervous system, circulatory system, and various organs, Campylobacter infections represent a serious public health concern. Campylobacter can be effectively combated by addressing the hygienic conditions in both food production and human lifestyles. Accordingly, the authors put forward a One Health perspective, which provides readers with essential insights into the basic biology of Campylobacter, as well as practical guidance on aspects ranging from food production to the clinical treatment of infections. Chapters 'Population Biology and Comparative Genomics of Campylobacter Species' and 'Natural Competence and Horizontal Gene Transfer in Campylobacter' are available open access under a Creative Commons Attribution 4.0 International License via link.springer.com.