

Introduction

HUNTINGTON'S DISEASE: A CLINICAL, GENETIC AND MOLECULAR MODEL FOR POLYGLUTAMINE REPEAT DISORDERS

It is now well over a century since George Huntington (figure 1), in a brief description of admirable clarity, delineated the main features of the neurodegenerative disorder that has since been known as Huntington's disease (HD) (Huntington 1872). Working as a family practitioner on Long Island, New York State, he drew on not only his own observations of the affected families under his care, but also on those of his father and grandfather in the same practice before him, covering a total period of 60 years.

Although limited to less than two pages, Huntington's description, later cited by William Osler as a model of clinical observation (Osler 1894), covered almost all of the key features of the disease. He noted the involuntary movements or 'chorea', the adult onset, the relentlessly progressive nature and fatal course of the condition and the progressive motor disability, as well as the loss of mental function and behavioural problems, these last often occurring from an early stage of the disease. He also recognized its familial nature, correctly stating that it did not normally skip generations.

It is worth noting in the context of a scientific meeting that not only was George Huntington's classical description brief, but it was the only scientific paper that he ever wrote. Despite this, his name is rightly remembered as having provided the foundations for the later detailed studies that have made, and continue to make, HD a model not only for the study of other neurodegenerative disorders but also for a wide range of aspects involving research and practice relating to genetic disorders, and now as the principal model for the study of the newly recognized group of polyglutamine repeat disorders.

During the century after Huntington's description, a wealth of detail was recorded on the clinical and neuropathological aspects of HD (Harper 1996). These studies showed clearly that it was a primary brain degeneration, with a rather characteristic distribution involving cell loss in parts of the basal ganglia and cerebral cortex, notably the caudate nucleus. No clear indications could, however, be obtained from pathological, clinical or experimental studies as to what might be the specific underlying cause of the disorder; increasingly, workers involved in HD research looked towards the developing field of genetics to provide the answers.

The inheritance of HD had been recognized as following an autosomal dominant pattern from the time that Mendel's laws had been rediscovered. Affecting both sexes equally, transmitted only by affected individuals (apart from those dying young), and with 50% of offspring of an affected parent developing the disorder, HD provided a striking example of this mode of inheritance, whereas its high frequency in many rapidly expanding immigrant populations of European origin made it a major problem in relation to genetic counselling and to prevention of the condition. However, puzzling genetic features were noted that did not fit with conventional Mendelian inheritance, notably the paternal transmission of the rare juvenile form of the disease (Merritt *et al.* 1969), and the recognition that 'anticipation', long recognized and debated in relation to another dominantly inherited disorder, myotonic dystrophy (Penrose 1948), applied also to HD, at least in the male line (Ridley *et al.* 1991). Until the gene was isolated, solutions to these questions remained the subject of speculation only.

Gene mapping was first attempted for HD in the 1970s, using blood groups and other protein markers, but was not then successful owing to the lack of power of these markers and the scarcity of large families with a sufficient number of living affected members. It was the advent of DNA polymorphisms, along with recognition of the value of the large and extended Venezuela kindred with HD, that made localization of the gene possible, added to which should be mentioned the foresight of the Hereditary Disease Foundation in supporting the long-term effort needed and in attracting high-quality scientific groups to work on the topic. In fact, the initial localization, to everybody's surprise, came much earlier than expected with the finding (Gusella *et al.* 1983) that one of the first DNA polymorphisms available clearly localized the gene to the short arm of chromosome 4.

From this point on, the eventual isolation and identification of the gene was never in doubt, even though it took ten years to achieve this goal (Huntington's Disease Collaborative Research Group 1993). It should be remembered that at the outset of the work in 1983, the actual isolation of a gene by positional cloning was entirely a conjecture rather than an established fact. Again, the formation of the Huntington's Disease Collaborative Research Group, its funding and its coordination and general nurturing by the Hereditary Disease Foundation through years of apparently slow progress, provide an object lesson on how a truly collaborative major scientific project can be sustained and ultimately succeed.

It should not be thought that the work of the Collaborative Group proceeded on a fixed plan; on the contrary, new techniques were introduced as they became feasible, whereas new ideas from other fields of

Glutamine Repeats And Neurodegenerative Diseases Molecular Aspects

Peter S. Harper, Max F. Perutz



Glutamine Repeats And Neurodegenerative Diseases Molecular Aspects:

Glutamine Repeats and Neurodegenerative Diseases Peter S. Harper, Max F. Perutz, 2001 This book focuses on the discovery of a common genetic basis for a group of inherited neurological disorders including Huntington's Disease, spinobulbar atrophy and a series of hereditary ataxias. This shared molecular background and other similarities have led to the development of theoretical models for the pathogenesis of these diseases. It is now also clear that the mechanisms involved are likely to be of more general relevance outside of this particular group of disorders with implications for other neurodegenerative processes such as those involved in Alzheimer's, Parkinson's and Prion diseases. The book is an edited and updated compilation evolving from a Royal Society discussion meeting.

Glutamine Repeats and Neurodegenerative Diseases Royal Society (Great Britain). Discussion Meeting, 1999

Glutamine Repeats and Neurodegenerative Diseases, 1999 *Molecular Mechanisms of Neurodegenerative Diseases* Marie-Francoise Chesselet, 2000-10-19 With the unprecedented identification of new mutation mechanisms in neurodegenerative diseases and the emergence of common mechanisms among diseases that were once considered unrelated, neurobiologists are poised for the development of new therapies based on high throughput screenings and a better understanding of the molecular and cellular mechanisms leading to neurodegeneration. In *Molecular Mechanisms of Neurodegenerative Diseases*, Marie-Francoise Chesselet MD PhD and a panel of leading researchers and neurologists from industry and academia critically review the most recent advances from different yet complementary points of view. Focusing on Alzheimer's, Parkinson's and CAG triplet repeat diseases, the authors show how studies of cellular and genetically engineered animal models have enhanced our understanding of the molecular mechanisms of neurodegenerative diseases and may lead to the development of new therapeutics. Topics include the role of Ab toxicity, glial cells and inflammation in Alzheimer's disease, the formation of abnormal protein fragments across several diseases, the impact of dopamine and mitochondrial dysfunction on neurodegeneration, and the potential of genetics to identify the molecular mechanisms of neurodegenerative diseases. Authoritative and insightful, *Molecular Mechanisms of Neurodegenerative Diseases* synthesizes the novel ideas and concepts now emerging to create a fresh understanding of neurodegenerative disorders, one that promises to lead to powerful new therapies that prevent, delay the onset, slow the progression or even cure these cruel diseases.

Molecular Aspects of the Stress Response: Chaperones, Membranes and Networks Peter Csermely, László Vigh, 2007-08-09 We are extremely happy to present the reader this book containing a summary of a well known research field, the phenomenon of cellular stress defense from two new angles: networks and membranes. The volume starts with an introduction to the concept of molecular chaperones in their original sense. R. John Ellis, the founder of the chaperone concept, describes chaperones as mediators of correct assembly and/or misassembly of other macromolecular complexes. This sets the tone of the book where later chapters give detailed examples of the richness of chaperone action by hundreds of other proteins and membrane structures. The reader will learn the role of chaperone

classes such as Hsp27 or Hsp90 the action of highly organized chaperone networks in various cellular compartments such as the ER or mitochondrial ER networks as well as the molecular details of the signaling mechanisms leading to chaperone induction during stress Various special stress defense mechanisms against oxidative stress or dryness will also be covered Membranes comprise a surprising mixture of stability and dynamics in the cell Their role in the regulation of the stress response has been accepted only slowly in the field Two chapters summarize this important aspect of the stress response showing the importance of membrane hyperstructures lipid species composition protein membrane interactions and cold adaptation

Glutamine Repeats and Neurodegenerative Diseases, 1999 **Progress in Nucleic Acid Research and Molecular Biology**, 2000-10-19 Nucleic acids are the fundamental building blocks of DNA and RNA and are found in virtually every living cell Molecular biology is a branch of science that studies the physicochemical properties of molecules in a cell including nucleic acids proteins and enzymes Increased understanding of nucleic acids and their role in molecular biology will further many of the biological sciences including genetics biochemistry and cell biology Progress in Nucleic Acid Research and Molecular Biology provides a forum for discussion of new discoveries approaches and ideas in molecular biology It contains contributions from leaders in their fields and abundant references Provides a forum for discussion of new discoveries approaches and ideas in molecular biology Features contributions from leaders in their fields Contains abundant references

Protein Quality Control in Neurodegenerative Diseases Richard I. Morimoto, Yves Christen, 2012-12-13 The health of the proteome depends upon protein quality control to regulate the proper synthesis folding translocation and clearance of proteins The cell is challenged constantly by environmental and physiological stress aging and the chronic expressions of disease associated misfolded proteins Substantial evidence supports the hypothesis that the expression of damaged proteins initiates a cascade of molecular events that leads to Alzheimer s disease Parkinson s disease amyotrophic lateral sclerosis Huntington s disease and other diseases of protein conformation Protein folding and misfolding: neurodegenerative diseases Judit Ovádi, Ferenc Orosz, 2008-12-21 Offering all the latest in the study of neurodegenerative diseases this book reviews the molecular events initiated by unfolded or misfolded proteins leading to conformational human diseases especially those found in Parkinson s and Alzheimer s diseases The Molecular and Genetic Basis of Neurologic and Psychiatric Disease Roger N. Rosenberg, 2003 Inside the third edition of this reference the reader will find thorough and authoritative discussions of all of these developments and their implications for clinical practice It includes a major new section on Psychiatric Diseases descriptions of the molecular and genetic basis of the spongiform encephalopathies as well as the expression of the prion gene under physiologic and pathologic conditions additional coverage examines the human genome project and neurologic disease and coverage on Alzheimer s disease and related dementias

The Ubiquitin-Proteasome System R. John Mayer, Aaron J. Ciechanover, Martin Rechsteiner, 2008-06-25 The second volume in a new series dedicated to protein degradation this book discusses the mechanism and cellular functions of targeted protein

breakdown via the ubiquitin pathway Drawing on the combined knowledge of the world's leading protein degradation experts this handy reference compiles information on the proteasome mediated degradation steps of the ubiquitin pathway In addition to proteasomal function and regulation it also presents the latest results on novel members of the ubiquitin superfamily and their role in cellular regulation Further volumes in the series cover the function of ubiquitin protein ligases and the roles of the ubiquitin pathway in regulating key cellular processes as well as its pathophysiological disease states Required reading for molecular biologists cell biologists and physiologists with an interest in protein degradation

Dopamine and Glutamate in Psychiatric Disorders Werner Schmidt, Maarten E. A. Reith, 2010-04-21 An illuminating summary of our current understanding of the interactive role of dopamine and glutamate in psychiatric diseases and the therapeutic strategies and possibilities for future treatment Among the new ideas presented are hypotheses on the role of dopamine and glutamate in aggression the glutamate system in anxiety disorders glutamate and neurodegeneration and on the origin and progression of Parkinson's disease Additional chapters offer novel insights into a variety of psychiatric diseases including ADHD stress aggression addiction schizophrenia depression social phobias dementias bulimia and neurodegenerative diseases like Parkinson's and Alzheimer's diseases Each chapter summarizes the prevalence and symptoms of the disease and explains the involvement of dopamine and or glutamate systems using the newer molecular approaches such as transgenic knockout or knockin mice and recent brain imaging techniques *Molecular Chaperones in Health and Disease* Matthias Gaestel, 2005-09-27 Molecular chaperones are involved in a wide variety of essential cellular processes in living cells A subset of molecular chaperones have been initially described as heat shock proteins protecting cells from stress damage by keeping cellular proteins in a folding competent state and preventing them from irreversible aggregation Later it became obvious that molecular chaperones are also expressed constitutively in the cell and are involved in complex processes such as protein synthesis intracellular protein transport post translational modification and secretion of proteins as well as receptor signalling Hence it is not surprising that molecular chaperones are implicated in the pathogenesis of many relevant diseases and could be regarded as potential pharmacological targets Starting with the analysis of the mode of action of chaperones at the molecular cellular and organismic level this book will then describe specific aspects where modulation of chaperone action could be of pharmacological and therapeutic interest **Analysis of Triplet Repeat Disorders** Michael Hayden, Dr David Rubinsztein, 2020-07-26 Analysis of Triplet Repeat Disorders is aimed at clinicians and scientists who work with these diseases or who have an interest in the field Using the clinical picture of these diseases as a starting point the book reviews and integrates the current understanding of their molecular pathologies the genotype phenotype relationships the mutational processes of trinucleotide repeats and the laboratory and clinical issues relating to genetic testing for these disorders **From Genotype to Phenotype** Sue Malcolm, 2001-11-19 This volume of the Human Molecular Genetics series covers such genotype phenotype correlations as clinical and environmental aspects

gene structure expression and mutation Also discussed are models of certain diseases and future prospects for treatment and prevention This book provides the reader with a basic overview of the physical expression of genetic disease before discussing in detail the most recent research and therapeutic developments *Current Topics in Developmental Biology* Gerald P. Schatten, 2005-11-09 *Current Topics in Developmental Biology* provides a comprehensive survey of the major topics in the field of developmental biology The volumes are valuable to researchers in animal and plant development as well as to students and professionals who want an introduction to cellular and molecular mechanisms of development The series has recently passed its 30 year mark making it the longest running forum for contemporary issues in developmental biology Includes information on the Zebrafish genetics and formation of embryonic vasculature Offers an analysis of muscle stem cells Provides data on diseases in the Drosophila fly Selection of 9 tables and 10 color figures *Huntington's Disease* Nagehan Ersoy Tunalı, 2012-02-15 Huntington's Disease is one of the well studied neurodegenerative conditions a quite devastating and currently incurable one It is a brain disorder that causes certain types of neurons to become damaged causing various parts of the brain to deteriorate and lose their function This results in uncontrolled movements loss of intellectual capabilities and behavioural disturbances Since the identification of the causative mutation there have been many significant developments in understanding the cellular and molecular perturbations This book *Huntington's Disease Core Concepts and Current Advances* was prepared to serve as a source of up to date information on a wide range of issues involved in Huntington's Disease It will help the clinicians health care providers researchers graduate students and life science readers to increase their understanding of the clinical correlates genetic aspects neuropathological findings cellular and molecular events and potential therapeutic interventions involved in HD The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines which collectively provide comprehensive description of the key issues in the area *Pathophysiology, Pharmacology and Biochemistry of Dyskinesia* Jonathan Brotchie, Erwan Bezard, Peter Jenner, 2011-09-19 Published since 1959 *International Review of Neurobiology* is a well known series appealing to neuroscientists clinicians psychologists physiologists and pharmacologists Led by an internationally renowned editorial board this important serial publishes both eclectic volumes made up of timely reviews and thematic volumes that focus on recent progress in a specific area of neurobiology research This volume reviews existing theories and current research surrounding the movement disorder Dyskinesia Leading authors review state of the art in their field of investigation and provide their views and perspectives for future research Chapters are extensively referenced to provide readers with a comprehensive list of resources on the topics covered All chapters include comprehensive background information and are written in a clear form that is also accessible to the non specialist *Huntington's Disease* Gillian Bates, Sarah Tabrizi, Lesley Jones, 2014-03-20 The fourth edition of the preeminent resource on Huntington's disease is a comprehensive resource on the current knowledge base surrounding this disease Comprising both updated chapters and

seven entirely new chapters it reflects the major advances that have recently occurred in our understanding of all aspects of this disease

Advances in Protein Chemistry and Structural Biology Alexander McPherson, 2010-09-09

Structural genomics is the systematic determination of 3 D structures of proteins representative of the range of protein structure and function found in nature The goal is to build a body of structural information that will predict the structure and potential function for almost any protein from knowledge of its coding sequence This is essential information for understanding the functioning of the human proteome the ensemble of tens of thousands of proteins specified by the human genome While most structural biologists pursue structures of individual proteins or protein groups specialists in structural genomics pursue structures of proteins on a genome wide scale This implies large scale cloning expression and purification One main advantage of this approach is economy of scale Examines the three dimensional structure of all proteins of a given organism by experimental methods such as X ray crystallography and NMR spectroscopy Looks at structural genomics as a foundation of drug discovery as discovering new medicines is becoming more challenging and the pharmaceutical industry is looking to new technologies to help in this mission

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