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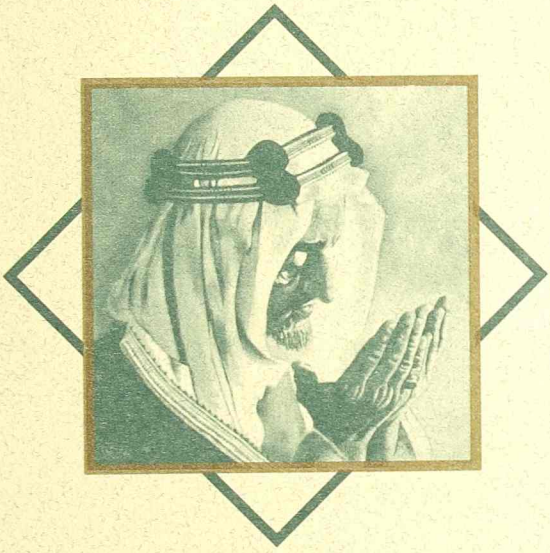
King Faisal International Prize



ARTICLES IN MEDICINE AND SCIENCE I

THE 1999 and 2000 KING FAISAL INTERNATIONAL PRIZE

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Custodian of the Two Holy Mosques

KING FAHD BIN ABD AL-AZIZ AL-SAUD

Patron of King Faisal Foundation

Since its inception, Islam has stressed the importance of knowledge and thought; hence the great encouragement and honour that scholars in Muslim countries have enjoyed over the centuries. Therefore, when the King Faisal Foundation enhanced its activities by establishing the King Faisal International Prize, it was following a well-established Islamic tradition.

It is my hope that such activities spread throughout the Arab and Islamic worlds and that these countries unite in order to realize the highest scientific and intellectual objectives.

Custodian of the Two Holy Mosques
King Fahd bin Abdul Aziz

(From King Fahd's address at the second annual ceremony of the King Faisal International Prize, 12 February 1980)

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INTRODUCTION

The King Faisal Foundation continues the traditions of Arabic and Islamic philanthropy, as they were revitalized in modern times by King Faisal. The life and work of the late King Faisal ibn Abd-Al-Aziz, son of Saudi Arabia's founder and the Kingdom's third monarch, were commemorated by his eight sons through the establishment of the Foundation in 1976, the year following his death. Of the many philanthropic activities of the Foundation, the inception of King Faisal International Prizes for Medicine in 1981 and for Science in 1982 will be of particular interest to the reader of this book. These prizes were modeled on prizes for Service to Islam, Islamic Studies and Arabic Literature which were established in 1977. At present, the Prize in each of the five categories consists of a certificate summarizing the laureate's work that is hand-written in *Diwani* calligraphy; a commemorative 24-carat, 200 gram gold medal, uniquely cast for each Prize and bearing the likeness of the late King Faisal; and a cash endowment of SR750,000 (UD$200,000). Co-winners in any category share the monetary award. The Prizes are awarded during a ceremony in Riyadh, Saudi Arabia, under the auspices of the Custodian of the Two Holy Mosques, the King of Saudi Arabia.

Since inception, the Prize for Medicine has been awarded eighteen times and has been shared among thirty-six recipients, while the Science Prize has been awarded fifteen times and has been shared among twenty-six recipients. Each year, a subcategory is established for the following year's awards. The Science subcategories have been broad: physics, biology, chemistry, biochemistry and mathematics. On the other hand, the Medicine subcategories have been more narrowly defined and have so far included primary health care, malaria, diarrheal diseases, viral hepatitis, diabetes mellitus, prevention of blindness, leukemia, infertility, schistosomiasis, coronary artery disease, acquired immunodeficiency, medical applications of genetic engineering, molecular immunology, management of the premature infant, degenerative diseases of the nervous system, control of communicable diseases, allergic diseases and aging. The 2001 Prize topic for Medicine will be "organ transplantation" and the 2001 Prize topic for Science will be "physics".

Nominations for the Prizes are accepted from academic institutions, research centers, professional organizations and other learned circles worldwide. After preselection by expert reviewers, the shortlisted works are submitted for further, detailed evaluation by carefully selected international referees. Autonomous, international specialist selection committees are then convened at the headquarters of the King Faisal Foundation in Riyadh each year in January/February to make the final decisions. The selections are based solely on merit, earning the King Faisal International Prize the distinction of being among the most prestigious of international awards to physicians and scientists who have made exceptionally outstanding advances which benefit all of humanity.

The most recent awards were presented in May 2000. Professor Cynthia Kenyon of the USA won the Prize for Medicine in recognition of her distinguished research in the field of aging. She has shown, for the first time, that aging is controlled hormonally through the insulin receptor system. Using a tiny nematode as an experimental model, she was able to make rapid advances in identifying the role of important genes that are conserved in higher species including man, and to make a detailed outline of the nature of aging, with a central hormone unit that integrates both environmental and intrinsic factors in the aging process. These findings indicate that aging is not an immutable process but one that might be amenable to hormonally-based therapeutic intervention. The Prize for Science (Biology) was shared by two destinguished scientists, both from the USA: Professor Edward O. Wilson and Dr. J. Craig Venter. Professor Wilson has made paramount contributions in many fields of biology, including ecology, conservation biology, behavioral biology and biogeography. He is the father of sociobiology and the founder of the modern biodiversity movement. Dr. Venter is one of the world's leaders in genome sequencing. Having pioneered novel techniques for rapid identification of genes and sequencing of entire genomes, Dr. Venter was the first to elucidate the entire genetic blueprint of a living organism, the preumonia-causing bacterium Haemophilus influenzae. This landmark achievement was soon followed by sequencing of entire genomes of other organisms, many of which were sequenced in Venter's laboratory. Recently, Dr. Venter and his team, together with researchers in the public-sector, have published the epoch-making sequence of the entire human genome.

This publication provides extensive further information about the work of these distinguished laureates and details their magnificant contributions to the advancement of science and medicine.

Khalid Al-Faisal
Chairman, The Prize Board
and
Director, King Faisal Foundation

WINNERS OF THE 1999
KING FAISAL INTERNATIONAL PRIZE
FOR MEDICINE

PROFESSOR PATRICK G. HOLT

Co-Winner of the 1999 King Faisal International Prize for Medicine

Photo: Professor Patrick G. Holt receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

Patrick G. Holt is Deputy Director and Head of the Division of Cell Biology at theTVW Telethon Institute for Child Health Research in Perth, Western Australia. He additionally holds an Adjunct Professorship in Microbiology at the University of Western Australia (UWA), and holds a career appointment as Senior Principal Research Fellow of the National Health and Medical Research Council of Australia. He additionally serves on the Scientific Advisory Boards of the Jenner Institute for Vaccine Research (UK) and the Cooperative Research Centre for Vaccine Technology (Brisbane, Australia), and is an International Councillor for the Society of Mucosal Immunology and for Collegium Internationale Allergologicum. He is currently on the Editorial Boards of Immunology, Clinical and Experimental Allergy, Pediatric Allergy and Immunology, Allergy, International Archives of Allergy and Immunology and *Journal of Immunology*.

Dr Holt was born in 1945 in the small town of Semaphore in South Australia, and moved to Western Australia soon after. He graduated dux of Christian Brothers College in the port city of Fremantle in 1962, and subsequently undertook a B.Sc. at UWA in Perth, followed by a Ph.D. in Biochemistry which was completed in 1969.

He interrupted his plans to take up a postdoctoral appointment in the U.S. for what was originally to be a temporary appointment as a Research Officer at the Department of Microbiology, UWA, in a research project on lung toxicology. This led to a growing fascination with the operation of the immune system in the respiratory tract, prompting eventually a full change of career path from Biochemistry to Immunology. He joined the Clinical Immunology Research Unit at Princess Margaret Hospital for Children in Perth in 1978 as Research Fellow, and won a career appointment with the National Health and Medical Research Council in 1987. He took up his present appointment in the Institute for Child Health Research in 1990.

Dr Holt is best known for the work originating in his laboratory on the regulatory mechanisms which control immune responses in the lung to inhaled antigens. Highlights from his extensive list of over 300 publications include (i) elucidation of the important immunomodulatory role of lung macrophage populations in relation to local expression of T-cell immunity; (ii) the discovery and characterization of the respiratory tract equivalent of the "Oral Tolerance" phenomenon, a process which selectively limits allergic sensitisation; (iii) the introduction of ELISPOT technology, which has revolutionised many areas of cellular immunology via provision of methods to quantitate T-cell and B-cell responses at the single cell level; (iv) the initial description and subsequent characterization of networks of antigen presenting dendritic cells throughout the respiratory tract - it is now widely believed that these cells play key roles in both the induction and expression of allergy, and as such they now represent major drug targets for the international pharmaceutical industry; (v) pioneering studies on the aetiology of allergic disease in humans, in particular recent work on the development of allergen-specific T_h-memory against dietary versus inhalant allergens

in atopics and non-atopics; of particular importance in this work has been the demonstration of a maturational defect in adaptive immune function which is associated with the atopic genotype and phenotype. The latter work has provided a framework for the development of novel strategies for primary prevention of allergic disease via early intervention during childhood; these include a specific "allergy vaccine" approach which is under investigation in several centres internationally.

REGULATION OF THE INDUCTION AND EXPRESSION OF IMMUNE RESPONSES IN THE LUNG

Patrick G. Holt

TVW Telethon Institute for Child Health Research,
Perth, Western Australia

The epithelial surfaces of the respiratory tract are continuously exposed to a wide range of airborne protein antigens which are ubiquitous in the natural environment. These include proteins on the surface of potentially pathogenic microorganisms (bacteria, viruses etc), but more commonly they are derived from non-pathogenic sources such as pollen grains, animal danders and insects. In order to maintain normal homeostasis in the lung, in particular at the blood/air interface, it is necessary for the respiratory mucosal elements of the immune system to accurately classify incoming antigens as pathogenic or non-pathogenic, and to develop and express local immune responses which are appropriate in both a quantitative and a qualitative sense, to the nature of the challenge antigen. In particular, it is vital that the local immune system does not mount strong and sustained responses to trivial antigens which are present continuously in the natural environment, in order to avoid the pathological consequences of chronic inflammatory damage to sensitive airway tissues such as that which is now recognised to underlie diseases such as allergic asthma.

At the time I became interested in these issues, in the late 1970s, immune regulation in the lungs *per se* represented one of the black boxes of medical research. Allergy was believed to stem from the combined effects of a failure in the barrier functions of mucosal tissues (such as secretory IgA antibody production) together with an intrinsically hyperactive immune system, resulting in the inappropriate induction of IgE antibody responses to antigens which were "ignored" in healthy individuals. Moreover, airways inflammation, in particular that resulting from allergy to inhaled antigens, was not widely accepted to play a significant role in the pathogenesis of asthma.

However, over the last 20 years, as a result of intensive research in this area on basic mechanisms of immune regulation in the lung by many groups, the importance of immunoinflammatory processes in diseases such as asthma is now recognised. It has also become clear that active immunological recognition of environmental allergens is virtually universal, and it is the type of immune response against allergens which determines whether individuals will express symptoms. Additionally, an expanding range of radically new prophylactic and therapeutic strategies for control of inflammatory airway diseases, which target a variety of these basic immunoregulatory mechanisms, are under development in many centres. The principal contributions of myself and my collaborators to the basic research underpinning these developments is summarized below, and encom-passes three related areas.

(i) Regulation of immune responses to inhaled antigens: characterisation of basic control mechanisms in experimental models

Studies in this area have focussed on both the induction of primary immunity to inhaled antigens in immunologically naive experimental animals, and on the expression of secondary immunity in the lung and airways in presensitized animals.

In the early 1980s, we set about to develop a "natural" model for allergic asthma in rats and mice, involving repeated exposure to aerosol mists containing an allergen, to mimic normal exposure in humans. The aim was to achieve allergic sensitization (in the form of IgE antibody production) and then study the cellular mechanisms involved in the sensitization process. Serendipitously, we instead found that it was virtually impossible to achieve persistent sensitization of animals via this route. Instead, they manifested biphasic low-level IgE responses which spontaneously "switched off" after a few weeks (1,2), and thereafter displayed a form of Tolerance which we later defined as Low Zone Tolerance or Immune Deviation. We further showed that this form of Tolerance conferred active long-term protection against allergic sensitisation against the specific allergen, and this protection could be mediated by both $CD4^+$ (3) and $CD8^+$ T-cells including those of the TcRγ/δ type (4- 6). More recent studies (7) suggest that the initial induction of this form of Tolerance is primarily regulated by antigen presenting Dendritic Cells within the airway mucosa, and that these regulatory T-cell populations effectively "police" the immune responses (via selective damping of Th2 responses) after the induction phase.

It is now recognised that immunologically naive humans (including infants) manifest an identical pattern of biphasic IgE production upon initial exposure to an allergen which they have not previously encountered, suggesting the operation of a similar set of regulatory mechanisms. These findings provided the impetus for the human studies.summarized in (iii) below.

In parallel with these studies, work has also proceeded on regulation of T-cell activation and control of secondary IgE responses within the lung, focusing on the role of pulmonary alveolar macrophages (PAM). Attention was initially drawn to the potential role of these cells in immune regulation in the lung in a landmark publication in 1978 (8), which was the flrst to demonstrate the lymphocytostatic properties of PAM in cultures of activated T-cells. The literature in this area is now extensive and is growing rapidly. Some of the key recent publications from my group in this area are (9-13). Collectively, they have provided the first direct evidence for an *in vivo* role for PAM in IgE regulation, via the demonstration that selective elimination of these cells from the lung leads to massive upregulation of local secondary responses to inhaled allergen. They further identify the dual cellular targets for PAM effects as T-cells and dendritic cells (DC). The T-cell effects are shown to involve a unique form of reversible anergy, which effectively limits the expression of T-cell immunity in the respiratory tract to a series of "single hits" via prevention of subsequent local clonal expression of the activated cells; human PAM are also shown to exert identical effects on T-cells. In our most recent study (14), the relevant molecular mechanism is identified as NO-mediated inhibition of intracellular signalling kinases in target T-cells.

(ii) Studies on lung and airway Dendritic Cell populations

The identification of populations of dendritic cells as "networks" throughout the epithelium of the conducting airways (Fig. 1) and the lung parenchyma, and their characterization as sentinel cells in surveillance for inhaled allergen/antigen, represents one of my group's most important contributions to the modern respiratory immunology literature. The first description of these cells in enzymatically disrupted lung suspensions, and the demonstration of their role as the principal resident antigen-presenting cell in these tissues, was made by us in the mid 1980s (15.16). The detailed functional characterization of these populations in experimental animals, and the formal demonstration of identical networks in human lung and airway tissues, has represented a major research priority in my lab, and some of the key findings are (17-24). Collectively, these characterize airway mucosal DC as a rapidly cycling sentinel population involved in sequestration and transport of inhaled allergen to T-cells in regional lymph nodes. Additionally, the airway DC network has been shown to be capable of rapid expansion during the early phase of the acute response to challenge with bacteria, viruses or allergen, thus further amplifying the efficiency of local antigen surveillance under conditions of stress; the participation of airway DC in the acute phase of local inflammatory responses suggests that they may provide the essential link between the innate and adaptive arms of the immune system.

In normal healthy airway tissue, DC are constrained from presentation of allergen *in situ* to local T-cells. One of the most important hypotheses arising from this work has been that a change of DC phenotype from "allergen sequestration/transport" to "allergen presentation" within the airway mucosa itself may herald the onset of chronic atopic asthma and/or rhinitis, and evidence in support of this suggestion is steadily accumulating in the literature. For this reason these DC have now been formally designated as high priority drug targets by several major pharmaceutical companies.

An additional series of findings, of major significance in relation to primary allergic sensitisation during infancy (discussed below), indicates that the postnatal maturation of these DC networks occurs very slowly in the airway mucosa, potentially compromising local immune function at several levels.

(iii) "Setting the seeds" for adult allergy during childhood: early postnatal development of T -cell memory against environmental allergens.

The initial impetus for these studies was the findings from the animal models ((i)above) which indicated that long term IgE-responsiveness to inhaled antigens was effectively "imprinted" into Th-cell memory during the first few rounds of exposure of the naive immune system. Extrapolating these findings to human, it was reasoned that immunological naivety to ubiquitous environmental allergens would in most cases be restricted to infancy, and hence early postnatal life was likely to be a key period for the determination of long-term allergen responder phenotype. Additionally, the animal studies suggested that mucosal "tolerance" mechanisms which protect against IgE responses in adult animals, function inefficiently during infancy. The key human observation which served as the final trigger for our work in this area was the initial claim in 1990 by a Japanese group that low-level allergen-specific lymphoproliferative responses could be detected in cord blood.

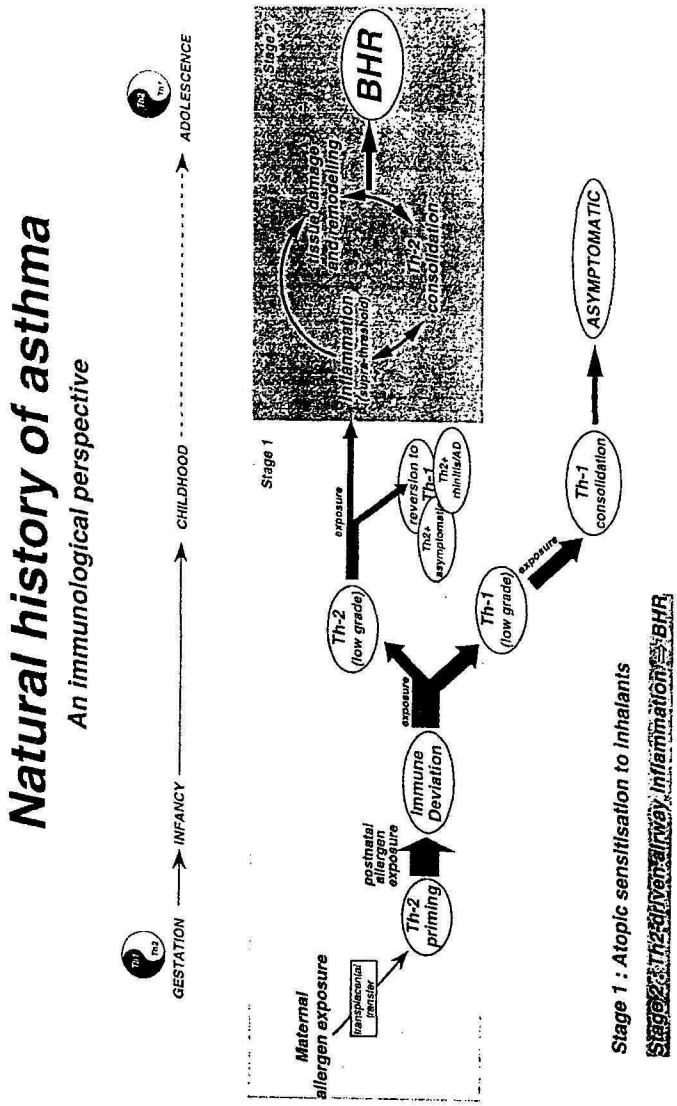

Fig.1: Airway intraepithelial Dendritic Cell (DC) network in rat tracheal epithelium.

Legend: Tangential frozen section cut parallel to epithelial basement membrane, providing an "en face" view of intraepithelial DC immunostained for MHC class II; comparable distribution is seen in human.

In the intervening period, my group has developed a major research program focusing upon allergen-specific T-cell immunity in humans during early life, which has provided important new insights into the aetiology of allergy at a number of different levels. The salient findings are (i) allergen-specific T-cell priming occurs transplacentally and is initially Th-2-polarized (25); (ii) postnatal regulation of responses to dietary and inhalant allergens follows divergent pathways resembling respectively high-zone versus low-zone tolerance (26-28); (iii) atopic children can become locked into allergen-specific cytokine reaction patterns equivalent to adults with chronic disease, before age 5 yrs (28-30); (iv) genetic risk for atopy is associated with delayed postnatal maturation of adaptive immune functions, especially Th-1-related functions (31-33); this important observation, initially made in studies on T-cell clones from atopic infants (28), has now been repeated in several labs with cord blood T-cells. Moreover, recent retrospective studies in my group have demonstrated this maturational defect in the cord blood of infants who subsequently develop allergy symptoms at age 2 years (29).

Potential implications of these studies

The information provided in the studies above has been integrated in a series of publications (34-37) into a theoretical framework which describes the natural history of allergy in immunological terms, from initial T-cell sensitization through to expression of chronic disease, in particular atopic asthma (Fig. 2). This synthesis has facilitated identification of potential "break points" in the early phase of the disease process, which serve as logical targets for primary prevention strategies, and this approach has stimulated wide ranging debate within the field. The most radical of these involves an active vaccination-like approach which aims to stimulate early Th-l-polarized immunity against allergens; other options include the early use of anti-inflammatory drugs to prevent the establishment of the self-sustaining "vicious cycle" of airways inflammation in atopic children, and the future development of treatment modalities to stimulate the rate of postnatal maturation of immune competence in "high risk" children. Related to the latter, this model also provides a logical framework for the testing of the "hygiene hypothesis" which has been advanced in many forms to explain the upsurge in allergy/asthma prevalence in developed countries since the 1960s. The theoretical explanation most commonly advanced to explain this phenomenon is the "T_h1-stimulatory" effects of respiratory tract infections, which are now less frequent and less severe in young children in developed countries. However, as argued in (38) and our more recent publications (37,39), the primary stimulus for the postnatal maturation of Th1-associated immune functions is exposure to microbial flora in the gastrointestinal tract. The possible contribution of gut flora to the allergic sensitization process is now under active investigation in several centres.

Fig. 2: Proposed natural history of atopic ashma from the immunological perspective.

Legend: Based on original scheme.

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PROFESSOR STEPHEN T. HOLGATE

Co-Winner of the 1999 King Faisal International Prize for Medicine

Photo: Professor Stephen T. Holgate receives his prize from HRH Prince Sultan ibn Abd Al-Aziz, Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

Stephen T. Holgate is a Medical Research Council Clinical Professor and Consultant Physician at the School of Medicine, University of Southampton.

Dr. Holgate was born on 2 May 1947 in Manchester. Although not directly from a medical family, his distant relative Viscount Christopher Addison was instrumental in founding the Medical Research Council (MRC) in the United Kingdom and was later to become its first Chairman. After completing his secondary schooling at King Edward VI School, Macclesfield, Cheshire, in 1965, Stephen Holgate entered Charing Cross Hospital Medical School, London, with an entrance scholarship. His interest in biochemistry rapidly became apparent and enabled him to transfer to an intercalated degree course on this subject, qualifying from the University of London with first class honours in 1968. He returned to his medical studies and received his Bachelor of Medicine and Surgery degrees in 1972, having been awarded both the Medical School's Llewellyn Scholarship and Clinical Gold Medial. Dr. Holgate completed his postgraduate clinical training at the London Postgraduate Hospitals which included the National Hospital for Nervous Diseases, Queen Square, and the Brompton Hospital before moving to Southampton where he undertook his specialist training in respiratory medicine. During this time he submitted his Doctorate of Medicine (MD) thesis on β_2 adrenoceptor resistance in human airways which was relevant to the overuse of bronchodilator drugs by asthmatic patients, so prevalent at that time. This experience also rekindled his research interest. In 1978 he was awarded a research fellowship by the MRC and Wellcome Trust to spend two years in Dr. K. Frank Austen's laboratory at Harvard Medical School, Boston, a move that was to set his course for a career in medical research.

After returning to the Department of Medicine at Southampton as a Senior Lecturer in 1980, he received a personal chair in 1986 and the following year was awarded one of five MRC Clinical Professorships to enable him to pursue research, a position he has held since.

Dr. Holgate is best known for his work on the inflammatory mechanisms of asthma. Beginning with an understanding of the importance of the mast cell as a source of bio-active mediators responsible for initiating inflammatory responses and airway dysfunction in asthma, his interest moved to studying eosinophils as the principal inflammatory cells responsible for the airway narrowing and tissue damage in chronic asthma, and T-lymphocytes in orchestrating the inflammatory response. However, frustrated by the lack of direct information about the roles that individual cells and mediators exerted in asthma, he was the first to apply fibreoptic bronchoscopy in order to obtain small amounts of airway tissue, and enabling asthmatic inflammation and the influence of known therapies to be studied directly in the affected organ. Key roles for small protein messengers (cytokines) and their cellular provenance were identified and the impact that these molecules had on recruiting eosinophils into the airways from the

circulation enabled a sequence of events leading to asthmatic inflammation to be deduced.

The importance of early allergen exposure in children at risk from asthma was identified as a major factor in the early life origins of childhood asthma and led to a number of cross-sectional and longitudinal studies in children exploring other environmental factors such as viruses and pollutants responsible for the expression and subsequent progression of the disease over time. A link with Dr. David Tyrrell FRS, then director of the MRC Common Cold Unit in nearby Salisbury, led to new polymerase chain reaction (PCR)-based methods for identifying common respiratory viruses, such as those that cause the common cold (rhinovirus) through their genetic make up, and in subsequent community and hospital based epidemiological studies a causative association was found between respiratory virus. He was awarded the 1999 King Faisal International Prize for medicine. In 1998 he was elected to the Academy of Medical Sciences as a Foundation Fellow.

Stephen Holgate lives in Romsey, Hampshire, with his wife Elizabeth, a practising nurse, and their two youngest children, Katharine and Michael. His other two sons, Matthew and Edmund, are in London, one working in the city at a finance house and the other completing his chemistry degree at King's College, London.

ASTHMA: A DYNAMIC DISCORDER OF INFLAMMATION AND REPAIR

Stephen T. Holgate

Medical Research Council Clinical Professor of Immunopharmacology
School of Medicine, University of Southampton

In 1860 Henry Hyde Salter, a London Physician, described asthma as a distinct entity characterised by episodic shortness of breath and wheezing. Over the 100 years that followed, the concept that asthma was an intermittent disorder involving airways smooth muscle led to the widespread development of the rapidly acting inhaled β-adrenoceptor agonists as symptom relieving therapy. While undoubtedly effective and popular amongst patients, the consequences of this approach became only too apparent during the late 1960's and early 1970's with epidemics of asthma mortality occurring in those countries where inhaled bronchodilators in high doses became easily available. When I entered asthma research in 1975, concern was already being expressed about the adverse consequences of regular high dose bronchodilator therapy. I was able to reveal that their use in this way led to loss of bronchodilator responsiveness both in the airways and systemically and also provided a basis for β_2 agonist dependency. During this period interest was being generated on the role of small molecules released in asthmatic airways which caused many of the symptoms of asthma (mediators). Mast cells, through their interaction with inhaled allergens via the allergic antibody immunoglobulin (Ig)-E, had already been identified as a major source of mediators including histamine, and the elusive slow reacting substance of anaphylaxis (SRS-A). Working at Harvard Medical School in Dr. K. Frank Austen's laboratory enabled me to define some key regulatory steps in the activation of mast cells by allergen, particularly the role of IgE-receptor linked adenylate cyclase, the identification of a new bronchoconstrictor mediator, prostaglandin (PG) D_2 and a role for extracellular adenosine released from stressed cells, in augmenting mast cell responses.

In children atopy, the predisposition to develop allergic responses involving IgE to common environmental allergens, was identified as a key risk factor for the development of asthma. The importance of allergen exposure early in life for the evolution of asthma was first demonstrated in a collaborative study with Thomas Platts Mills from Charlottesville in which the level of dust mite exposure during the first year of life was shown to be an important predictor of whether or not an atopic child subsequently developed asthma and at what age. However, if progress was to be made in understanding how mediator pathways contributed to airway dysfunction in allergic disorders, a greater understanding of human mast cells was needed. This required establishing methods to disperse and purify mast cells from human lung and skin. Both mucosal and skin tissue mast cells proved to be important sources of PGD_2 as well as its active metabolite $9\alpha,11\beta$-PGF_2, both of which were powerful bronchoconstrictors acting via thromboxane (TP_1) receptors. Confirming studies on

rodent mast cells, activation of both human mast cells and basophils resulted in the rapid stimulation of adenylate cyclase. Despite claims that cell membrane phospholipid methylation pathways linked to IgE signalling were important in mast cell activation, we were unable to confirm this either in rodent or human mast cells. However, human mast cells and basophils were highly responsive to adenosine and its analogues which, at low concentrations, enhanced IgE-dependent mediator release through an effect on cell surface A_{2B}-purinoceptors. Adenosine proved to be a powerful bronchoconstrictor of asthmatic but not normal airways, an action enhanced by the adenosine uptake inhibitor dipyridamole and inhibited by anti-asthma drugs including xanthines, sodium cromoglycate and corticosteroids. The use of drugs with well defined pharmacological actions enabled us to incriminate the mast cell in different types of asthmatic response. Inhaled β_2-agonists and sodium cromoglycate inhibited early allergen-induced bronchoconstriction (EAR), while critical roles for histamine, PGD_2 and the cysteinyl leukotrienes were also revealed. A clear role for mast cell mediator release was shown for attacks of asthma provoked by exercise, hyperventilation and inhalation of hypertonic aerosols. The late asthmatic response (LAR) and the attendant increase in airway responsiveness after allergen exposure reproduces more closely naturally occurring asthma.

In the mid-1980's it was known that eosinophils were selectively recruited into the airways during the LAR but the mechanisms involved were not known. The ability of sodium cromoglycate and nedocromil sodium to inhibit both the EAR, LAR, as well as the circulating leucocyte response to allergen, provided evidence for the involvement of mast cells in leukocyte recruitment during the LAR. In sensitised guinea pigs we were able to demonstrate the role played by eosinophils and T cells in the LAR, however, while this and other animal models could be used to study relatively acute airway inflammatory events, they were not models of chronic asthma.

In 1987 the passage of a small amount of fluid into the airways (lavage) was already being used to obtain a more direct picture of the underlying inflammatory events in asthma. Rigid bronchoscopy had been used to obtain bronchial biopsies but this procedure required general anaesthesia and could not be used widely. To gain access to asthmatic lungs, we pioneered the use of fibreoptic bronchoscopy enabling cellular and molecular studies to be undertaken on tissue from patients with asthma of different types and severity. The key role played by mast cells and eosinophils in the inflammatory response was confirmed, as well as the engagement of selective adhesion molecules expressed on the airway blood vessels and epithelium which were involved in the recruitment of eosinophils and other leukocytes from the circulation that underpinned asthmatic inflammation. Using small biopsies, we were able to describe the pattern of epithelial damage and associated deposition of sub-basement membrane collagen types I, III and V in association with fibronectin. These repair proteins are deposited by myofibroblasts as a consequence of epithelial injury and provided evidence that asthma was a chronic disorder of repair as well as inflammation. Analysis of tissue samples before and after treatment with the anti-asthma drugs, inhaled corticosteroids theophylline and long acting β_2 agonists enabled us to deduce how these drugs work on the underlying inflammatory response.

In 1990 Marshal Plaut, at Johns Hopkins School of Medicine, Baltimore, reported that mast cells from the mouse could generate and release small cell signalling proteins (cytokines). In a series of biopsy studies we were able to show that human mast cells were also an important source of tumour necrosis factor alpha (TNFα), interleukin (IL-4) and IL- 5, three cytokines critically involved in eosinophil recruitment by upregulating the expression of adhesion molecules and serving as leukocyte chemoattractants. The relative distribution of these cytokines between mucosal and connective mast cell subtypes differed, adding to the concept that not all mast cells were the same and that the local microenvironment was critical in determining their ultimate function. When activated via their IgE receptors, highly purified human mast cells expressed increased gene expression for TNFα, IL-4 and IL-5 which was followed by release of the cytokine proteins over 48-72 hours. The quantity and time course of cytokine secretion by activated mast cells provided an explanation for eosinophil recruitment during the allergen-induced LAR and has helped place mast cells at the centre of the allergic tissue response.

In severe asthma, the sentinel role played by T lymphocytes was shown by their increased number in the airways of patients who had died from this disease. Death from asthma was associated with increased central and peripheral airway inflammation which would greatly impair the ability of the lung to serve as ventilatory organ. In chronic severe asthma characterised by frequent night time attacks, eosinophils were shown to preferentially infiltrate the alveoli and peripheral airways in the early hours of the morning, associated with both T cell influx and the release of the pro-allergic cytokines, IL-4 and IL-5.

When considering the interface between the external environment and the lung, the principal target for the inflammatory attack in asthma is the bronchial epithelium (Fig 1). The major site of damage is the junction between the columnar and basal cells with disruption of desmosomal and other adhesion junctions which weakens the epithelium and at the same time facilitates access of inhaled allergens, viruses and air pollutants. We have also found evidence that the asthmatic epithelium is altered in the direction of a "repair" response. Firstly, there is increased expression of cell surface markers of repair such as CD44 and epidermal growth factor receptors (EGFR). Secondly, inducible genes within the epithelium that encode mediators or their synthetic enzymes are over expressed including nitric oxide synthase, cyclooxygenase 2 and endothelin-l. Thirdly, the epithelium also becomes a major source of cytokines and chemokines which serve to augment the airway inflammatory response. Finally, the epithelium secretes growth factors for fibroblasts and smooth muscle which are involved in airway wall remodelling and bronchial hyperresponsiveness characteristic of chronic asthma.

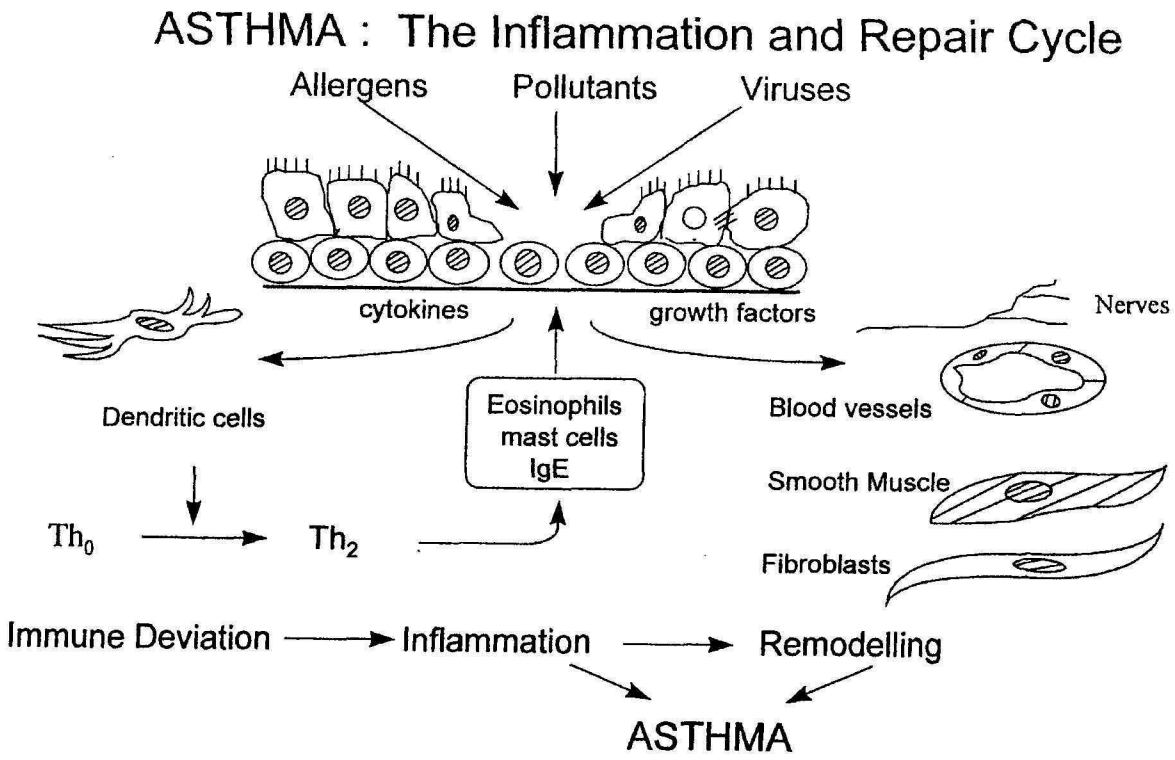
ASTHMA : The Inflammation and Repair Cycle
Allergens
Pollutants
Viruses
cytokines
growth factors
Nerves
Dendritic cells
Eosinophils
mast cells
IgE
Blood vessels
Smooth Muscle
Th0
Th2
Fibroblasts
Immune Deviation
Inflammation
Remodelling
ASTHMA

Fig. 1

An altered bronchial epithelium also helps explain why exposure to respiratory viruses and ambient air pollutants causes worsening of asthma. We established novel gene-based detection methods for respiratory viruses responsible for the common cold and, when applied to epidemiological studies, revealed that the majority of asthma episodes in children and adults were virus-related, the common cold viruses (especially rhinoviruses) accounting for more than half of these. The seasonality of viral episodes and the number of asthma admissions to hospital corresponded closely to the occurrence of community-acquired infections, and were especially prominent shortly after returning to school from vacations, presumably due to new respiratory viruses being introduced and passed on within the school environment. To investigate mechanisms of virus-induced asthma we used the experimental infection protocols originally developed by Dr. David Tyrrell FRS, then Director of the MRC Common Cold Laboratory in nearby Salisbury. In young adult asthmatic volunteers, a common cold was induced under controlled conditions and the airway cellular and mediator responses followed. Replicating virus in the nasal and bronchial epithelium were demonstrated accompanied by enhanced eosinophilic inflammation. Further studies showed that chemokines, cytokines and other mediators released from the infected epithelium created a mechanism for virus enhancement of asthmatic airway inflammation.

Application of fibreoptic bronchoscopy to study the airway effects of exposure to the outdoor and indoor air pollutants ozone (O_3), oxides of nitrogen (NO_x) and particulates has shown both acute and more chronic inflammatory effects. Short term O_3 exposure in healthy normal volunteers caused acute respiratory symptoms through the release of neuropeptides from sensory nerves which is then followed by increased expression of endothelial adhesion molecules and inflammatory cell influx involving neutrophils and T cells. Since exposure to NO_2 and diesel exhaust also produces a neutrophil mediated inflammation, a final common pathway to explain the toxic action of air pollutants is likely to involve oxidant injury to the respiratory epithelium, activation of the nuclear transcription factor $NF\text{-}\kappa B$ and subsequent secretion of a range of proinflammatory mediators and cytokines in a manner not dissimilar to those mechanisms also utilised by respiratory viruses.

The recognition that asthma is a chronic inflammatory condition of the airways accessible to prevention and pharmacological intervention has had a major impact in underpinning national and international guidelines on modern disease management. The knowledge that inhaled corticosteroids control airway inflammation and should be used as primary therapy while short acting inhaled β_2-bronchodilators relieve breakthrough symptoms, has enabled us to formulate self management plans in which patients are able to exert greater control over their asthma care. Since 1993 the progressive decrease in asthma mortality in England and Wales may in part be due to the effective introduction of asthma guidelines that were introduced in 1990 when the anti-inflammatory action of inhaled corticosteroids became known. Although inhaled drugs are the mainstay for the asthma treatment, the recent introduction of leukotriene receptor antagonists (LTRAs) as highly selective orally active agents represents the first new drug class available to treat asthma for over 20 years. Cysteinyl leukotrienes interact with other proinflammatory mediators to cause airway narrowing. Of special relevance is their role in aspirin-induced asthma in which we have found a marked and

selective upregulation of the terminal enzyme involved in cysteinyl leukotriene synthesis, LTC_4 synthase.

Recognising that genetic susceptibility and environmental exposure are both prerequisites for developing allergic diseases such as asthma, efforts are underway to identify novel susceptibility genes. Our approach has been to use a combination of microsatellite genotyping, candidate gene approaches and new methods to capture the complexities of the asthma and allergy phenotypes. We have found highly significant linkage or allelic association to regions on chromosomes 5, 6,11,12 and 14.

Our research into the cellular and molecular mechanisms of asthma has led to the concept illustrated in Figure 2. In genetically susceptible subjects, asthma evolves from environmental exposure most commonly to domestic allergens. Over time the disease either regresses or becomes influenced by further environmental factors including allergen exposure, virus infection, air pollutants and diet that determines the eventual clinical asthma phenotype in pattern, chronicity, severity and responsiveness to treatment. Since, in many subjects destined to develop asthma, these processes begin early in life, it follows that effective environmental and therapeutic interventions should be started as soon as the diagnosis of asthma is made in order to prevent disease progression.

Asthma : The Natural History

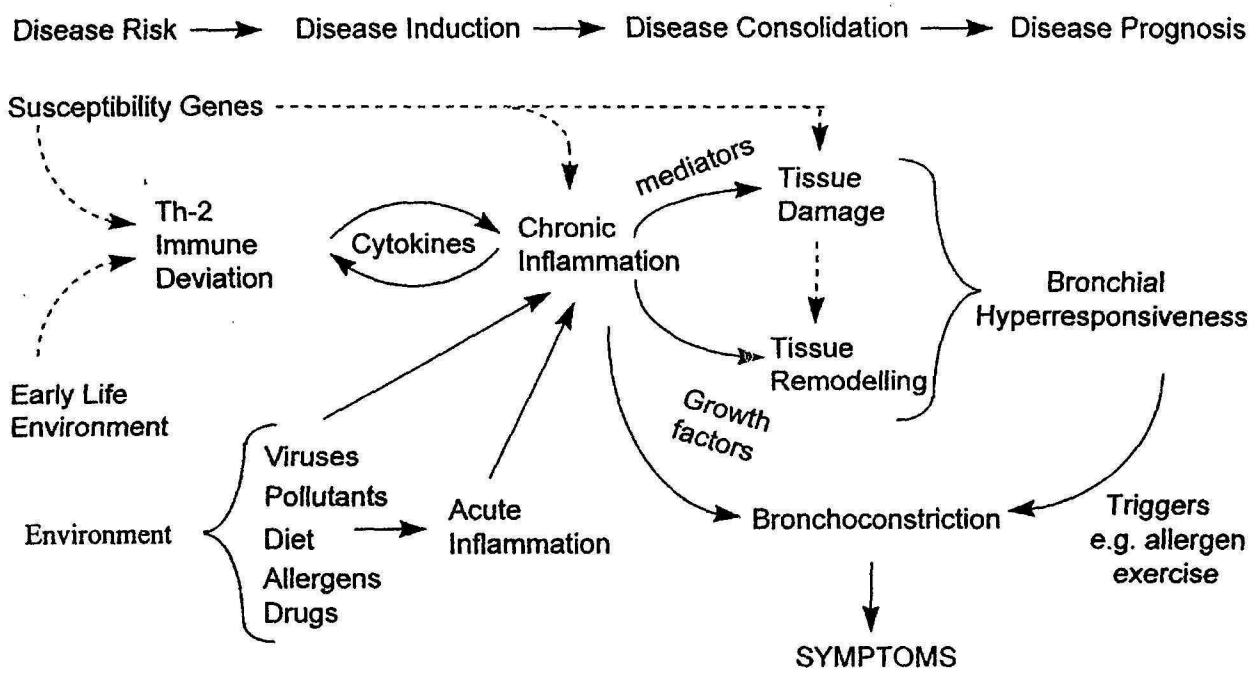

Fig. 2

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Winners Of The 1999
King Faisal International Prize
For Science

PROFESSOR RYOJI NOYORI

Co-Winner of the 1999 King Faisal International Prize for Science

Photo: Professor Ryoji Noyori receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

Ryoji Noyori is Professor of Chemistry, Nagoya University, Japan. Dr. Noyori, a native Japanese, was born on September 3, 1938 in Hyogo Prefecture. He is the first son of Dr. Kaneki Noyori, a successful industrial chemist, and Suzuko Noyori. Dr. Noyori attended an elementary school attached to Kobe University and then Nada Middle and High School in Kobe. As a youth, he participated in many sports. Under the influence of his father's profession, Dr. Noyori became interested in chemistry at a young age and he started to study organic chemistry at Kyoto University under the guidance of Professor Keiiti Sisido, obtaining his Bachelor's degree in 1961. He completed his Master's degree in 1963 and immediately became a Research Associate (Instructor) in Professor Hitosi Nozaki's laboratories at Kyoto. Dr. Noyori received his Ph.D. degree in 1967. Earlier, in 1966, Drs. Nozaki and Noyori found the first example of a homogeneous asymmetric reaction catalyzed by transition metal complexes. It was then that they discovered asymmetric cyclopropanation of styrene with diazoacetates in the presence of a small amount of a chiral Schiff base-Cu complex, albeit with a low enantioselectivity.

In 1968, Dr. Noyori was appointed Associate Professor in the Department of Chemistry at Nagoya University. He began to focus on organic synthesis via organometallic chemistry in his new research group. In 1969-1970, Dr. Noyori spent a postdoctoral period with Professor E. J. Corey at Harvard University. Shortly after returning to Nagoya he was promoted to Professor in 1972. Currently Dr. Noyori is Dean of the Graduate School of Science at Nagoya University and a Member of the Scientific Council of the Ministry of Education, Science, Sports and Culture. He served as President of the Society of Synthetic Organic Chemistry , Japan, from 1997 to 1999 and was Director of the ERA To Molecular Catalysis Project of the Japan Science and Technology Corporation from 1991 to 1996. Dr. Noyori is a Fellow of the American Association for the Advancement of Science and an Honorary Member of the Chemical Society of Japan.

Dr. Noyori has contributed to the progress of modern chemistry in many ways. He is best known for his initiation and development of asymmetric catalysis using organometallic molecular catalysts. The efficiency of the asymmetric catalysts discovered by Dr. Noyori rivals or in certain cases even exceeds that of enzymes. Applications of his original and versatile chemistry have allowed him and other scientists to achieve truly efficient synthesis of organic molecules of theoretical and practical importance and technical refinements have led to the industrial production of biologically and physiologically significant substances. His major accomplishments in stereoselective synthesis include the invention of a chirally modified lithium aluminum hydride reagent and its application to prostaglandin synthesis; the invention of the atropisomeric BINAP ligand and asymmetric synthesis of amino acids using a BINAP-Rh complex; the synthesis of (-)-menthol based on BINAP-Rh catalyzed asymmetric isomerization of geranylamine to citronellal enamine; the establishment of the three-component asymmetric synthesis of prostaglandins; the discovery of highly

enantioselective addition of dialkylzincs to aldehydes catalyzed by chiral amino alcohols; the discovery of asymmetric hydrogenation of olefins catalyzed by BINAP-Ru complexes; the practical asymmetric synthesis of biologically active substances based on BINAP-Ru catalyzed hydrogenation; the discovery of asymmetric hydrogenation of functionalized ketones catalyzed by BINAP-Ru complexes; the demonstration of the general utility of dynamic kinetic resolution in asymmetric catalysis; the elucidation of the molecular mechanism of the chirality amplification phenomenon in organozinc chemistry; the discovery of a carbonyl-selective hydrogenation method and its extension to asymmetric hydrogenation of aromatic and olefinic ketones; the invention of chiral Ru catalysts effecting highly selective asymmetric transfer hydrogenation of ketones and imines. In particular, Dr. Noyori's BINAP chemistry has been utilized worldwide in research laboratories and also on an industrial scale.

Dr. Noyori's accomplishments are not limited to asymmetric synthesis. Recently, he demonstrated for the first time the remarkable utility of supercritical carbon dioxide as a medium for homogeneous catalysis. He showed its own fixation by Ru catalyzed hydrogenation to produce formic acid, methyl formate, and dimethylformamide with extremely high turnover numbers. He also developed practical, environmentally sound methods for olefin epoxidation and alcohol oxidation using aqueous hydrogen peroxide, allowing direct conversion of cyclohexene to adipic acid.

Dr. Noyori's iron carbonyl-polybromo ketone reaction, discovered during his early days in Nagoya, allows the construction of five- and seven-membered carbocycles in a [3 + 2] and [3 + 4] manner, respectively. He exercised initiative in the catalytic use of organosilicon compounds for organic synthesis. In addition, Dr. Noyori explored a series of synthetic methodologies using organocopper, -tin and -zinc reagents for selective carbon-carbon bond forming reactions. The combined use of these reactions with his original asymmetric reduction of ketones has resulted in the long-sought convergent synthesis of prostaglandins. He also achieved the first truly efficient synthesis of solid-anchored DNA oligomers using organopalladium chemistry.

His scientific contributions have been recognized with, among others, The J. G. Kirkwood Award (1991), The Asahi Prize (1993), The Tetrahedron Prize (1993), The Japan Academy Prize (1995), The Arthur C. Cope Award (1997), and now The 1999 King Faisal International Prize for Science. He was honored as a Person of Cultural Merit in 1998.

Dr. Noyori lives in Nagoya with his wife Hiroko. Their first son, Eiji, is an active journalist, and their second son, Koji, is studying painting.

ASYMMETRIC CATALYSIS: SCIENCE AND OPPORTUNITIES

Ryoji Noyori

Professor of Chemistry and Dean of the Graduate School of Science,
Nagoya University, Japan

Molecules possess a fixed elemental composition with definite bonding of their components and a defined relative and absolute stereochemistry, the latter being referred to as chirality (handedness). Chemists now can determine precise molecular structures and synthesize molecules with desired properties. Over the last three decades, I have devoted myself to the exploration of efficient chemical methods, particularly for the stereoselective synthesis of a range of organic molecules of both theoretical and practical importance.

Molecular chirality is a principal element that plays a key role in science and technology. A wide range of biological and physical functions involves precise molecular recognition that requires matching of chirality and other steric and electronic factors. Enzymes, receptors, and other binding sites in living systems interact selectively with right- or left-handed organic molecules, called enantiomers, thereby generating various reactions involved in metabolism and numerous biological responses. Optical and electronic processes also occur by means of highly ordered assemblies of chiral molecules. Until the early 1970s, the classical resolution of racemates (equimolar mixtures of enantiomers) was the primary method used to obtain pure enantiomers. Other methods involve the transformation of readily available natural chiral compounds such as amino acids, tartaric and lactic acid, terpenes, carbohydrates, and alkaloids. Prior to the mid 1970s, practical access to pure enantiomers from non-chiral compounds was possible only by using biochemical or biological methods employing enzymes, cell cultures, or whole microorganisms. The scope of such approaches is limited because many biological processes exhibit single-handed, lock-and-key specificity. Chemical synthesis, on the other hand, is characterized by generality and flexibility. Thus, discovery of truly efficient chemical methods for obtaining chiral substances, referred to as asymmetric synthesis, is a substantial challenge for scientists.

Figure 1 illustrates a general principle of *asymmetric catalysis* which provides an ideal method for synthesizing enantiomeric compounds. Among the various possibilities, use of chiral metal complexes as homogenous molecular catalysts is one of the most powerful strategies. This chemical approach, which uses a small amount of a synthetic chiral catalyst, produces natural or unnatural chiral compounds selectively and in large quantities. The ligands that modify intrinsically achiral metal atoms must be endowed with suitable electronic properties and three-dimensional structures to generate the desired stereoselectivity. To achieve maximum chiral efficiency, chemists must create efficient catalytic systems that permit precise discrimination among enantiotopic atoms,

groups, or faces in achiral molecules. Certain well designed chiral metal complexes not only accelerate the chemical reactions of the associated molecules but also differentiate between stereochemically different transition states with an accuracy of 10 J/mol. It is in this way that such compact molecular catalysts with molecular weights less than 1000 (<20 Å in length or diameter) provide an ideal method for chemical multiplication of chirality. The diverse catalytic activities of metallic species, as well as the virtually unlimited structural variation of the organic ligand, provide enormous opportunities for asymmetric catalysis. Recent advances in this area are turning chemists' dreams into reality at both the academic and industrial levels.

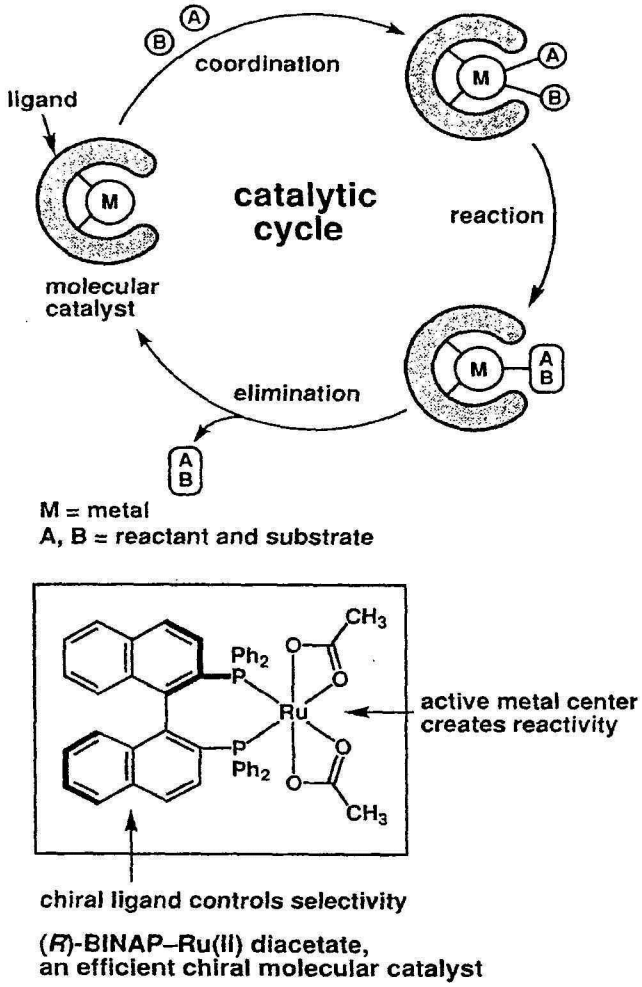
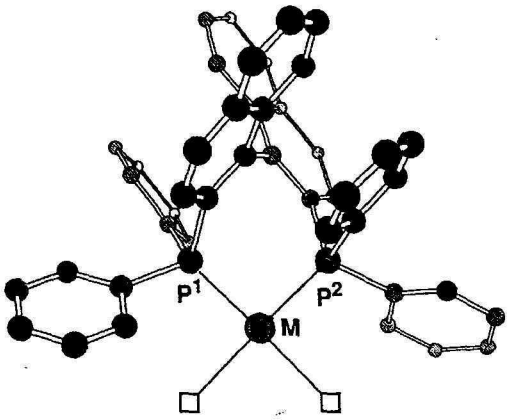


Figure I. The general principle of asymmetric catalysis with organometallic molecular catalysts. Catalysts which consist of a metal atom or ion and organic or inorganic ligands present a general strategy for selective chemical transformations, because of the diverse reactivities of the metallic elements and the unlimited structural permutability of organic ligands. The metallic centers provide reactive sites, whose reactivity and selectivity are fine tuned by the surrounding ligands. The advantage of such molecular catalysts is highlighted in asymmetric catalysis by organometallic complexes with chiral organic ligands. The electronic and steric properties of the organic ancillaries have a strong effect on the course of reactions, so selection of central metals and careful molecular design of the chiral ligands are particularly important for efficient asymmetric catalysis. A well designed chiral catalyst can combine A and B, producing stereoselectively the chiral compound AB in a large quantity.

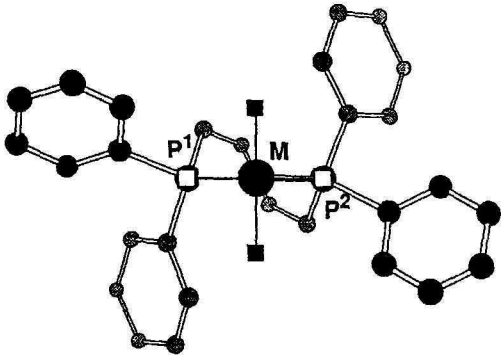
More than thirty years ago, when I was in Professor H. Nozaki's Laboratory at Kyoto, we discovered the first example of homogeneous asymmetric catalysis using a structurally well defined transition metal complex, although this resulted from research being done for a completely different purpose. When a small amount of a chiral Schiff base-Cu(II) complex was used as a catalyst in the reaction of styrene and ethyl diazoacetate, *cis*- and *trans*-cyclopropanecarboxylates were obtained with one enantiomer in a slight excess (only 10 and 6%, respectively). At that time the degree of enantioselection was not of practical significance, but this Cu-catalyzed asymmetric cyclopropanation later allowed for the industrial synthesis of cilastatin, an in vivo stabilizer of the carbapenem antibiotic, imipenem (Sumitomo Chemical Co./Merck Co.).

Later at Nagoya, we focused largely on development of efficient asymmetric hydrogenation because reduction of unsaturated compounds is one of the most fundamental chemical reactions. In 1980, together with Professor H. Takaya, we invented a new chiral ligand, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), which opened a new era in the field of asymmetric catalysis. Its transition metal complexes are remarkably effective in various kinds of asymmetric catalyses. For instance, BINAP-Rh(1) complexes catalyze the asymmetric hydrogenation of various dehydro amino acid derivatives to give both natural and unnatural amino acids of high enantiomeric purity. More significantly, our discovery in 1986 of asymmetric hydrogenation using the BINAP-Ru(II) complex catalysts provided a major breakthrough in stereoselective organic synthesis. The scope of this method is far reaching. The BINAP-Ru(II) dicarboxylate complexes serve as excellent catalysts for the highly enantioselective hydrogenation of various unsaturated carboxylic acids and dehydro amino carboxylic or phosphonic acid derivatives. For example, (*S*)-naproxen (an anti-inflammatory agent) and (*S*)-2-methylbutanoic acid (a fruit flavor) are readily accessible by this method. This enantioselective hydrogenation has pemitted the general asymmetric synthesis of isoquinoline alkaloids including morphine, various benzomorphans, and morphinans including dextromethorphan (an anticough agent). Furthermore, asymmetric hydrogenation of geraniol or nerol allows for the large scale synthesis of citronellol. This method is also suitable for the synthesis of vitamins E and K_1 and 1β- methylcarbapenem antibiotics. Kinetic resolution of racemic 4-hydroxy-2-cyclopentenone has provided easy access to the *R* enantiomer, an intermediate in prostaglandin synthesis, on a multi-kg scale (Teijin Co./Takasago International Co.).

Notably, in the presence of BINAP-Ru complexes, a wide range of functionalized ketones can be hydrogenated to chiral secondary alcohols with a consistently high enantiomeric purity. This chemical approach is far superior to any of the biological ones, because the hydrogenation can be performed cleanly on any scale with a very high substrate concentration of up to 50% inorganic solvents. This method is currently used for the industrial synthesis of antibacterial levofloxacin (Daiichi Pharmaceutical Co.) and for the production of a chiral azetidinone intermediate for carbapenem antibiotics (Takasago International Co.). Other important applications include the synthesis of carnitine (a carrier of long-chain fatty acids through cell membranes), an intermediate for compactin (an HMG-CoA reductase inhibitor), of the statine series (a component of the human renin inhibitor), of DOPS (an anti-Parkinsonian agent), and of fosfomycin (an antibiotic). The chiral efficiency of BINAP chemistry was found to originate from unique dissymmetric templates created by transition metal elements and the C_2 chiral diphosphine, as illustrated in Figure 2.



top view



side view

M = metal
□ = coordination site within the P^1–M–P^2 plane
■ = coordination site outside of the P^1–M–P^2 plane

Figure 2. Schematic representation of the chiral environment of (*R*)-BINAP-transition metal complexes. As seen from the side view of the template where the naphthalene rings are omitted for clarity, the seven-membered λ-structured ring is highly skewed. This dissymmetry determines the chiral array of the four phenyl rings attached to the phosphorus atoms, which in turn differentiate clearly the two sets of quadrant sectors. Owing to the steric shielding by the phenyl substituents, the second and fourth quadrants are much more crowded than the first and third quadrants. The degeneracy caused by C_2 symmetry minimizes the number of possible reactive intermediates and transition states. The simple, well-shaped molecular catalysts display remarkable efficiency in stereoselective chemical reactions that occur in the inner and outer coordination spheres of the templates.

More recently, we started a new phase of research in this field. Most existing homogenous and heterogeneous hydrogenation catalysts preferentially saturate C=C bonds over C=O bonds. In 1995, our laboratories developed a new $RuCl_2$ (diphosphine)(1,2-diamine) catalyst which allows for the long-sought C=O selective hydrogenation. This method is ideal for the large scale reduction of ketones to alcohols because of the low cost of the catalyst, operational simplicity, and environment friendliness. The system, consisting of a chiral diphosphine such as BINAP and a chiral 1,2-diamine, is the most practical asymmetric catalyst. Reactivity and selectivity of the Ru catalysts can easily be perturbed by electronic and steric effects (bulkiness and chirality) of the phosphine and diamine ligands. This hydrogenation method has an exttemely broad scope of applications, exhibiting promise for the practical asymmetric synthesis of a wide range of chiral alcohols from aromatic and olefinic ketones. In addition, this reaction is highly productive and very rapid. For example, the asymmetric hydrogenation of an aromatic ketone has achieved a turnover number, defined as mols of product per mol of catalyst, as high as 2 400 000 and a turnover frequency of 228 000 h^{-1} or 63 s^{-1}. This method is applicable to the synthesis of intermediates of vitamin E, anthracyclin antibiotics, and carotenoid-derived bioactive substances and odorants.

Molecular hydrogen is obviously the most conventional hydrogen source for hydrogenation. Recently, however, our new concept on the reaction mechanism has resulted in a range of asymmetric reductions using stable organic donors such as 2-propanol and formic acid in the presence of novel chiral Ru(II) complexes. A variety of chiral alcohols and amines can be obtained from ketone and imine precursors, respectively. These procedures provide a useful complement to catalytic reduction for small- to medium-scale reactions. Its utility has been demonstrated by the asymmetric synthesis of building blocks of MK-0417 (a carbonic anhydrase inhibitor) and L-699,392 (an LTD_4 antagonist) as well as many isoquinoline and indole alkaloids.

At present a number of academic and industrial research laboratories utilize our BINAP chemistry to produce significant chiral compounds. Importantly, a fruitful collaboration with Professor S. Otsuka's group in the early 1980s revealed that BINAP-Rh(I) complexes could effect the asymmetric isomerization of allylic amines to enamines. The (S)-BINAP-Rh catalyzed isomerization of allylic amines to enamines. The (*S*)-BINAP-Rh catalyzed isomerization of diethylgeranylamine to (*R*)-citronellal enamine on a scale of nine tons is the world's largest industrial application of asymmetric catalysis. This process is utilized for the production of a variety of optically active terpenes such as (–)-menthol (Takasago International Co.).

In the late 1970s, we elaborated a chirally modified lithium aluminum hydride reducing agent that exhibits extremely high enantioselection in the reduction of a wide variety of ketones. This reagent is remarkably effective in generating the 15*S* stereochemistry of the prostaglandin series, facilitating their commercial synthesis (Ono Pharmaceutical Co.). In addition, a variety of organocopper, -tin, and -zinc reagents allowing selective carbon-carbon bond forming reactions were also developed in our laboratories. In fact, the combination of these methodologies and BINAP chemistry in 1985 realized the long-sought three-component synthesis of prostaglandins. Thus, for example, a prostaglandin E_1 derivative can be obtained stereoselectively in one pot by combining a chiral five-membered block and two side chain units. This new method allows for a

practical synthesis of natural and unnatural prostaglandins that include therapeutically significant isocarbacyclin. This straightforward chemical synthesis is now widely used for advanced biochemical and physiological studies of prostaglandins. For example, we developed the antitumor Δ^7 -prostaglandin A^1 methyl ester and structurally more elaborate analogues, an azido-functionalized prostacyclin analogue (APNIC) which acts as a photoaffinity probe for the prostacyclin receptor, and 15*R*-TIC which has very high binding affinity and selectivity for a prostacyclin receptor in the central nervous system.

Development of efficient chiral multiplication methods for the organometallic reaction of carbonyl compounds constitutes a genuine challenge. In 1986 we succeeded in the first highly enantioselective addition of dialkylzincs to aldehydes with the aid of a catalytic amount of a camphor-derived amino alcohol, DAIB, opening a new area of asymmetric catalysis. This asymmetric reaction exhibits a unique, enormously nonlinear effect, in terms of the enantiomeric purity of the chiral source and alcoholic products. Typically, the reaction using DAIB in an enantiomeric ratio of 58:42 forms the alkylation product in an enantiomeric ratio of 98:2, which is close to the 99:1 ratio obtained with enantiomerically pure DAIB. The origin of this striking chiral amplification has been elucidated at the molecular structural level. It is based on the self- and nonself recognition of asymmetric catalysts and this phenomenon is now proved to be a general one. This study may shed light on the mechanism of the propagation of chirality in nature.

Thus, the discovery and recent growth of asymmetric catalysis have opened tremendous potential for stereoselective chemical synthesis. Selective synthesis of single enantiomers has become a common practice in laboratories. Homogeneous asymmetric catalyses are also significant industrially, particularly in the production of pharmaceuticals, agrochemicals, flavors, and fragrances as well as in the creation of advanced materials. I am very pleased to be involved in and contribute to the progress of this important scientific field.

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PROFESSOR DIETER SEEBACH

Co-Winner of the 1999 King Faisal International Prize for Science

Photo: Professor Dieter Seebach receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

Dieter Seebach is Professor of Chemistry in the Laboratory of Organic Chemistry, the Chemistry Department of the Swiss Federal Institute of Technology in Zürich, Switzerland.

Born 1937 in Karlsruhe, Germany, as first child of Kurt Seebach, a teacher of ancient languages, and his wife Erika, Dieter Seebach grew up and visited elementary schools in several small towns where the family had been evacuated to, in the turmoil of the last years of world war II. He then attended a classical-education secondary school in Karlsruhe, from which he graduated in 1956. Early on he developed an avid interest in chemistry, converting the washhouse in his parent's home into a laboratory, at the age of 14. Thus, it was with no hesitation that he chose to study chemistry at the Technische Hochschule and University of Karlsruhe, graduating in 1961, and receiving the doctoral degree in 1964 with a thesis on small-ring and peroxide chemistry, carried out under the supervision of Rudolf Criegee.

Dr. Seebach then moved to the United States (1965/66) to do postdoctoral work with Elias J. Corey and to join the Harvard Chemistry Department in Cambridge, Massachusetts, as a lecturer. It was during this period when a new synthetic method was developed, which is now referred to as the Corey-Seebach reaction.

After his return to Germany, Seebach started an independent university carreer in Karlsruhe, and he became a full professor of organic chemistry at the *Justus-Liebig-Universität* in Giessen in 1971 where he held Liebig's chair and was Director of the Institut für Organische Chemie, also chairing the department for one term, until 1977. In those years the principle of reactivity *umpolung* (now a chapter in organic-chemistry textbooks) has been developed and demonstrated with numerous examples. Research in the field of enantioselective synthesis started in Giessen (chiral solvents and additives, reductions with baker's yeast, tartaric acid as a chiral building block), and the term "chiral pool" was coined there. During this period Seebach held two half-year visiting professorships in the USA (University of Wisconsin, Madison, and California Institute of Technology, Pasadena).

In 1977, Dr. Seebach was offered to come to ETH Zürich as successor of Vlado Prelog, who had won the Nobel prize two year before, in recognition of his contributions to sterochemistry. The team of strong colleagues (Arigoni, Dunitz, Eschenmoser, Jeger, Oth, and Simon) who did research and tought in the organic division, the superb spirit of the place, the equipment and research support, the excellent students of the institution, and the fruitful contacts with the pharmaceutical industry in Basel added up to an irresitable incentive for Seebach to move from Germany to Switzerland. Seebach has been at ETH ever since, also serving for two terms as head of the Laboratorium für Organische Chemie and for one term as Chairman of the Department of Chemistry.

During the first years in Zürich the interaction with the chemical crystallographer *Jack Dunitz* led to solid-state structure determinations of functionalized organolithium compounds (Li enolates, Li dithianes), and Seebach's group succeeded in identifying by NMR spectroscopy the species present in solution of lithium derivatives (including so-called carbenoids) which are central to organic synthesis. Simultaneously, natural-product syntheses were performed (macrodiolides such as elaiophylidin, gloeosporon, myxovirescin), the work on oligo- and polyhydroxybutyrate (PHB) was started, the principle of self-regeneration of stereocenters (SRS) was recognized and executed with α- and β-amino- and -hydroxy- carboxylic acid derivatives, back-bone modifications of peptides were achieved, and a new class of chiral ligands, the TADDOLs, was invented which have turned out be of general utility for syntheses of a variety of enantiomerically pure compounds.

In recent years, the research interests of Dr. Seebach have been shifting towards bioorganic and supramolecular chemistry, as well as material science: The role of short -chain polyhydroxybutyrates in biology (ion-channels through planar or liposomal phospholipid bilayers) was demonstrated, establishing the existence of a fifth class of biomacromolecules (besides proteins, nucleic acids, polysaccharides, and polyisoprenoids). The structure of chiral dendrimers (molecules containing branches, resembling those of trees) and their use for the synthesis of polymers with unusual properties *(cf.* high-performance polymer-bound catalysts) are being studied. A most important new research area is the investigation of β-peptides, homologs and analogs of α-peptides and proteins, the functional molecules of life. Contrary to predictions and expectations of the community of peptide and protein specialists, it turned out that short-chain β-peptides form all the secondary structures (helices, sheets, turns) known to be formed by longer-chain α-peptides and proteins! Furthermore, β-peptides are totally stable to peptidases, and are therefore promising candidates for the development of new drugs.

All these activities require a team of dedicated coworkers, as well as interdisciplinary collaborations, and they have led to numerous publications. The results obtained by the group have been described in more than 600 papers and in ca. 125 Ph.D. theses. In recognition of his achievements, Dr. Seebach was elected member of academies (Deutsche Akademie der Naturforscher Leopoldina, Halle; Akademie der Wissenschaften und der Literatur, Mainz, Germany; Schweizerische Akademie der Technischen Wissenschaften), he received an honorary Ph.D. degree (University of Montpellier, France), and many awards were bestowed upon him, such as the Karl-Ziegler-Preis (Gesellschaft Deutscher Chemiker), the Centenary Lecture Award (Royal Society of Chemistry, UK), the Fluka Prize for the Reagent of the Year (Switzerland), the Award for Creative Work in Organic Synthesis and the Roger Adams Award in Organic Chemistry (both of the American Chemical Society).

Besides teaching, supervising research, writing papers, and serving the department, frequent travelling is a major task for Dr. Seebach, as for any scientist of our days; lectures on research results have to be given (over 750, so far), many of which involve whole series of presentations, such as the JSPS visit to Japan, the Korea Lectures (Seoul National University), the Andrews Lectures (University of New South Wales, Australia), the Rolf-Sammet Lectures (Universität Frankfurt), and the Baker Lectures

(Cornell University). In view of all the professional activities, there is little time left for the many hobbies Seebach has, but he is uncompromising about taking his daily swimming exercises, whenever and wherever possible.

Dr. Seebach lives in Zürich, at walking distance from his laboratories, with his wife Inge; they have two sons (Jörg and Lutz) and a daughter (Petra), ages 33, 27, and 30. The oldest son is a researcher at the University Hospital in Zürich, specializing in immune medicine, the youngest is also a medical doctor, and Petra is a junior manager in a fashion company.

FROM PEROXIDES TO SYNTHETIC METHODOLOGY AND STEREOSELECTIVITY TO β- AND γ- PEPTIDE HELICES

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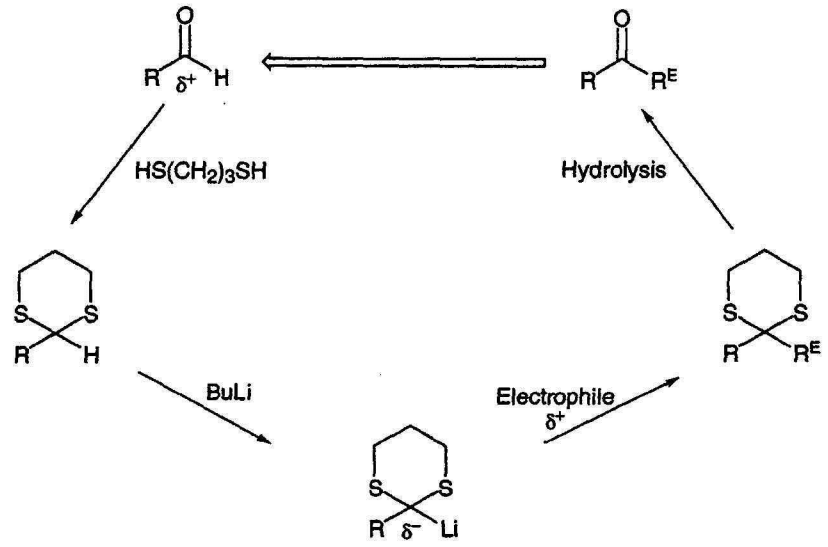
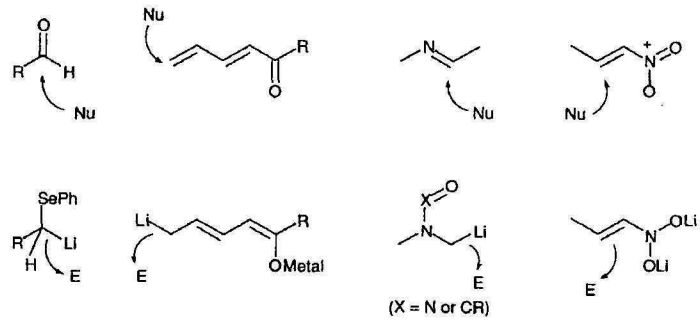
After having completed Ph.D. work in the area of mechanistic organic chemistry *(peroxides and valence isomerizations of cyclobutenes)*[1], I was introduced to the field of synthetic organic chemistry during postdoctoral work at Harvard University where the dithiane method was invented (Scheme 1)[2].



Scheme 1 *The Dithiane Method.* An aldehyde is converted to a 1,3-dithiane which is subject to lithiation in the 2-position, thus making possible the reaction with an electrophile. After hydrolysis, a ketone is isolated which has formally resulted by coupling of two electrophilic centers.

It involves the reversal of reactivity *(umpolung)* of an aldehyde formyl group and is now one of the standard methods of C,C-bond formation in the synthesis of complex compounds, especially of natural products[3]. Recognition of the general principle of

umpolung[4] led to the development of new synthetic methodology which enables the chemist to build molecules by coupling pre-cursors in unusual ways (Scheme 2).

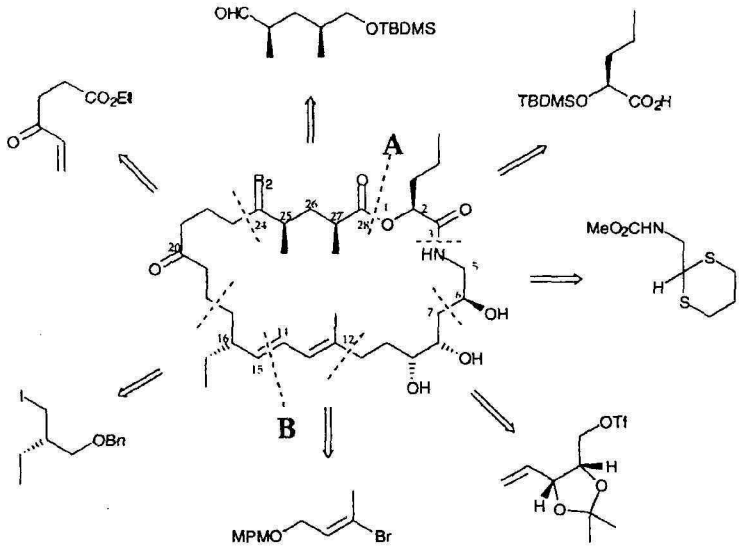


Scheme 2. *Reactivity Umpolung of Carbonyl Compounds and Analogs* Aldehydes, dienones, imines and nitroolefins react with nucleophiles in the specified positions. This inherent reactivity of these central building blocks of organic synthesis can be reversed through the lithiated derivatives shown.

Thus, two carbonyl carbons of the same electrophilic reactivity can be coupled by converting one of the reactants to a phenylseleno lithium reagent[5]. Double lithiation of certain unsaturated ketones leads to a reversal of the acceptor reactivity of a dienone in the 5-position[6]. The inherent electrophilic reactivity of imino groups is reversed in lithiated nitrosamines and amides[7], and double deprotonation of nitroalkanes furnishes nucleophilic super-enamines, in an umpolung of the nitroolefin acceptor properties[8].

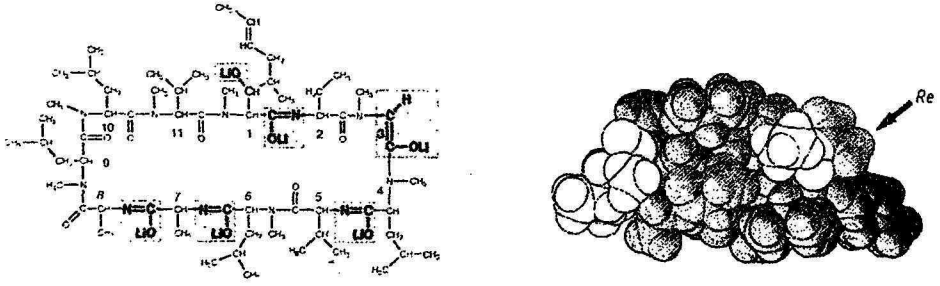
A new synthetic method still has to undergo the acid test of being applicable to *natural-product synthesis*. Therefore, part of our group was devoted to this goal, and we had chosen macrocyclic lactones and dilactones (so-called macrolides and macrodiolides) as our preferred targets. Over the years, we synthesized the antibiotics[9] pyrenophorin, vermiculin, grahamimycin, colletodiol, conglobatin, elaiophylidin, and myxovirescin (Scheme 3)[10], as well as the fungicide gloeosporone[11].

Along another line of work, we learned to achieve *backbone modifications of peptides* by multiple deprotonation, a process considered impossible, nay insane to even try! Experts in the field expected cleavage and isomerization of peptides under the conditions required for enolate formation of a constituent glycine residue, and they predicted unsurmountable solubility problems. We found that at dry-ice temperatures (-78°C) the strongest known bases (such as t-BuLi) can be employed for polylithiation and alkylation of peptides[12], and that solubility in the non-polar aprotic solvent THF can be mediated by addition of large amounts of lithium salts[13]. An application of this method[14] to Sandimmun® and Neoral®) is the immunosuppressive drug used worldwide to prevent rejection of transplanted organs and to treat certain autoimmune diseases. More than a hundred derivatives of this life-saving compound (produced in a biotechnological process) have been prepared under the conditions elaborated by us.



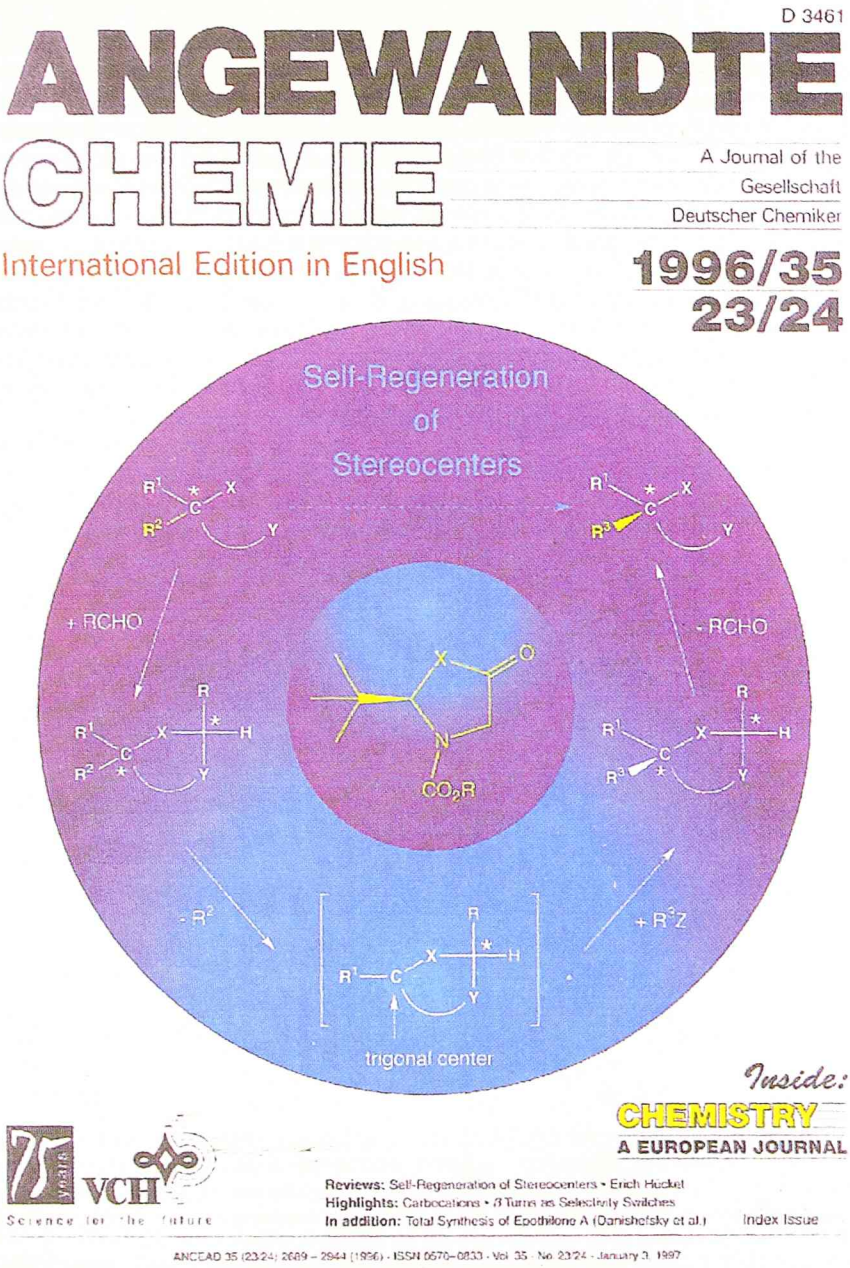
(Bn = $PhCH_2$, MPM = 4-MeO-$PhCH_2$, TBDMS = $^tBuMe_2Si$, Tf = CF_3SO_2)

Scheme 3. *Retrosynthetic Scheme for the Synthesis of the Natural Product Myxovirescin M2, an Antibiotic.* Several methods developed in our laboratory were employed in the synthesis, such as a dithiane reaction, Br /Li and I/Li exchange, and *Kolbe* coupling by electrolysis of a malic acid derivative.



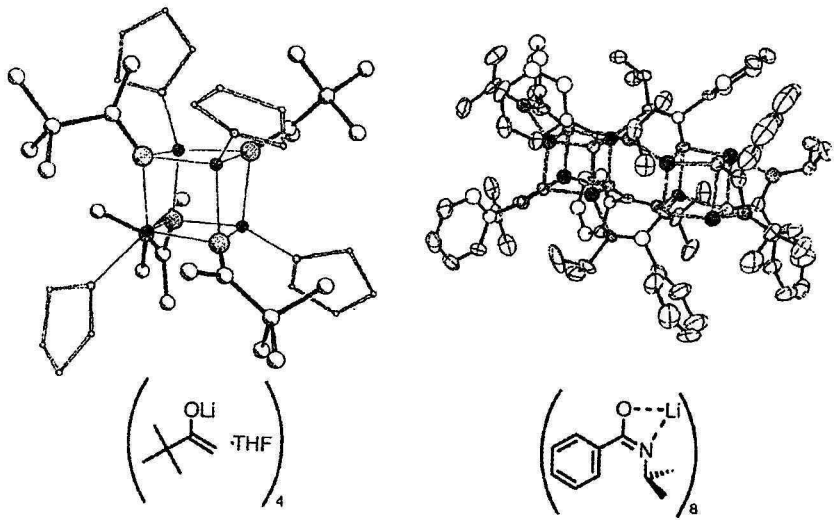
scheme 4. *Backbone Modification of the Immunosuppressive Drug Cyclosporin A through a Hexalithio Derivative.* Under carefully controlled conditions peptides can be polylithiated, with fonnation of sarcosine (or glycine) enolate moieties which react with electrophiles. In the case of cyclosporin A, a cyclic undecapeptide of molecular weight *ca.* 1200 Da, a single hydrogen atom (see arrow) on aminoacid 3 is thus replaced by electrophilically introduced groups in a stereoselective transfonnation, through a hexa-lithio derivative.

There are numerous natural and unnatural compounds with a tertiary stereogenic center, and it is a difficult task for the synthetic chemist to create such centers stereoselectively. It occurred to us that we could possibly use the readily available hydroxy and amino acids (from the *pool of chiral building blocks*[15]) as starting materials for the synthesis of enantiopure compounds *(EPC)* of this type. The problem was that the necessary annihilation of the single chirality center in these acids would inevitably lead to racemic products. Thus, we converted the acids to cyclic acetal derivatives which contain a second stereocenter, so that trigonalization of the original chirality center creates a reactive intermediate which is still chiral and which reacts diastereoselectively to re-generate a stereocenter at the carbon which was stereogenic to begin with (Scheme 5). We designate the overall process as *self-regeneration of stereocenters (SRS),* because no chiral auxiliary is required. After having recognized the principle, we demonstrated its viability with many examples, and SRS is now a widely used method[16]. Furthermore, the reactions employed for the execution of the principle (largely Li enolate chemistry) turned out to be so effective that we used them also for achiral precursors, such as the amino acid glycine; the corresponding heterocyclic acetals were obtained by resolution[16]. One of the applications is the preparation of isotopically labeled amino acids for medical diagnoses and analyses of drug metabolyses[16].



Scheme 5. *Self-Regeneration of Stereogenic Centers*. A temporary chirality center is used for enantioselective alkylation of 2-amino-, 2-hydroxy- and 2-mercapto-carboxylic acids at their one and only stereogenic center. Work in this area has also led to the development of chiral glycine derivatives for amino acid syntheses.

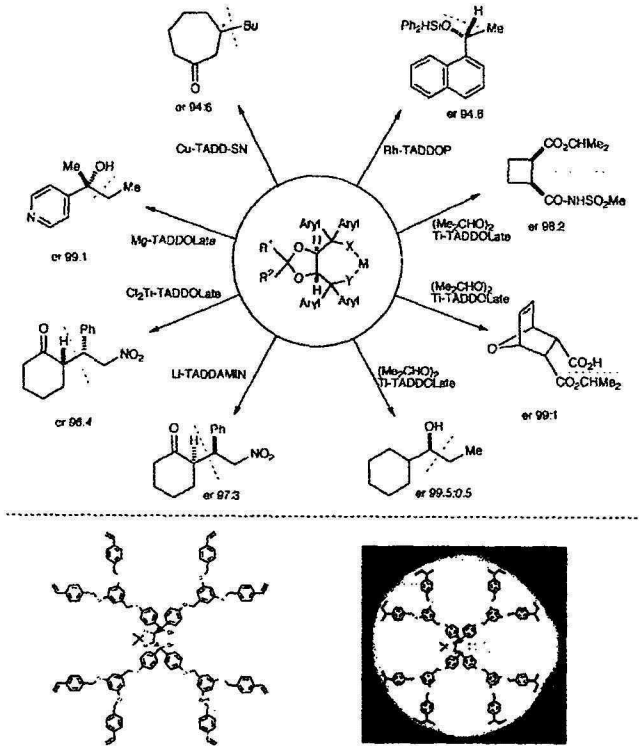
The work on reactivity *umpolung*, on natural product synthesis, on peptide modification, and on SRS relied heavily on the use of lithium compounds. For decades, organic chemists used the term "carbanion chemistry" to refer to such polar alkali (and alkaline earth) organometallic reagents, a choice of words suggesting that reactions of these nucleophilic species involve free carbanions, and omitting the role of the metal. There was a huge amount of know-how and there were myriads of applications of organoalkali, and especially of the lithium compounds, deposited in the chemical literature[17]. On the other hand, structural investigations had been carried out only with hydrocarbon derivatives (RLi), but not with the much more interesting and synthetically important heteroatom-substituted ones *(cf.* RO, RS, R_2N, F, Cl, Br, I on the lithiated carbon, Li enolates *etc.*). Thus, we embarked on an endeavour to determine the *structures of functionalized Li compounds* in solution (by NMR spectroscopy)[18] and in the solid state (by X-ray crystallography).[19,20] The crystal structures were determined (in a collaboration with J. D. Dunitz) by low-temperature techniques for isolation, recrystallization, and data collection with the air-sensitive and thermally unstable samples. Perhaps the most important result of these studies was the realization that all these Lireagents form aggregates (Scheme 6), which my be involed in the product-forming steps in solution[19]. This has been amply confirmed in subsequent years.[21]



Scheme 6. *Crystal Structures of Li Derivatives, a Li Enolate Tetramer and a Li Carboxamide Octamer.* Low-temperature generation, isolation, and X-ray analysis of synthetic Li reagents have opened the door for better understanding of their reactivity and selectivity. The work in this area is a demonstration of improved reactivity control with increasing complexity of the reagents.

In order to be able to compare polar main-group with early-transition-element organometallic compounds we began to study *titanium derivatives*, twenty years ago. Transmetalation of RLi or RMgX with $ClTi(OCHMe_2)_3$ furnished highly functional-group-selective and stereoselective new reagents.[22,23] From dramatic effects of the R'O groups in $R\text{-}Ti(OR')_3$ on the reactivity we quickly turned to chiral derivatives, and

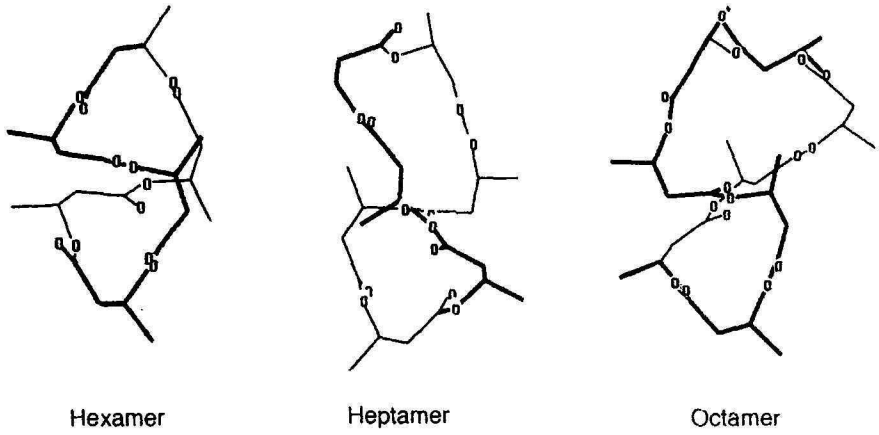
we tested several readily available enantiopure alcohols R'OH to form titanate reagents. To reduce the aggregation tendency we prepared a bulky diol from tartrate acetonide and phenyl Grignard reagent which became the prototype of a large family of chiral ligands for metal centers (Li, Mg, Al, Ti, Zr, Rh, Pd, Cu, Zn), *the TADDOLs* (abbreviation of the full name: $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl- 1,3-dioxolan-4,5-dimethanol). Some *reactions mediated by TADDOL derivatives are presented in the upper part of Scheme* 7; a short review article[24] covers the literature up to mid 1994. Most recently, we have prepared styryl-substituted TADDOLs for copolymerization with styrene and preparation of polymer-bound complexes.[25] The dendritic cross-linkers shown on the bottom of Scheme 7 gave polymers with unique material properties and performance in *multiple uses of the corresponding Ti complexes.*[26] -Besides being versatile chiral ligands for metals, TADDOLs can also be used as chiral NMR shift reagents,[27] for enantiomer-differentiating crystallization of inclusion compounds[28] and as chiral dopants for converting achiral liquid-crystals into cholesteric phases.[29]



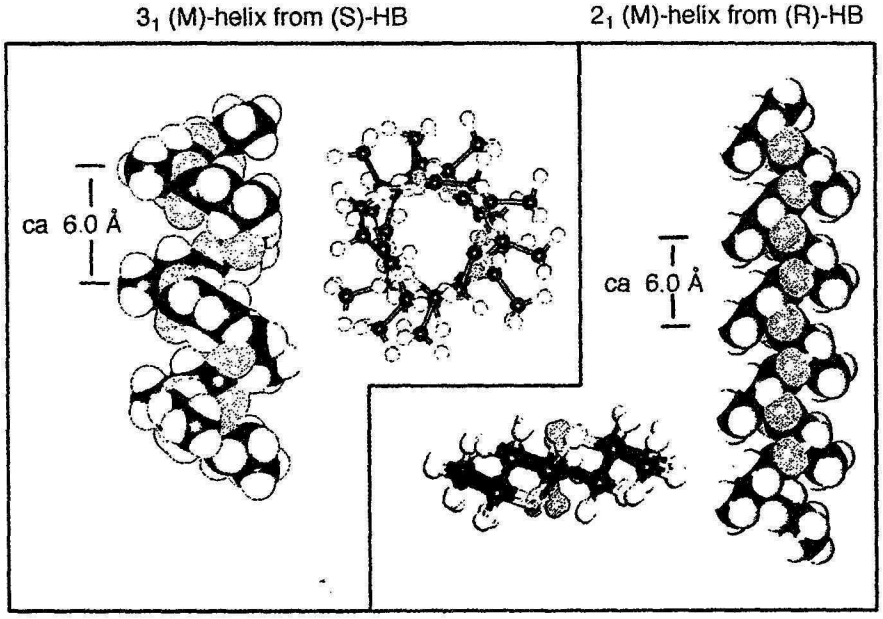
Scheme 7. *TADDOL a Versatile Auxiliary for the Preparation of Enantiopure Compounds, also on Solid Phase.* Top: Examples for the use of the tartaric-acid-derived TADDOL ligand in stoichiometric and catalytic transformations involving metal complexes. Bottom: TADDOL with dendritic branches for cross-linking polymerization and the derived polymer-bound titanium complex for heterogeneous catalysis; such novel types of polystyrenes, formed with dendritic cross linkers and carrying a central chiralligand, may be useful for high-performance multiple applications in enantioselective catalysis, as demonstrated for the first time with the TADDOL shown here. The background of the schematic presentation of the dendritic polymer-bound Ti- T ADDOLate (bottom right) is a microscopic photograph of an actual Ti-loaded polymer bead!

All our research projects have so far originated with a synthetic goal or problem. Thus, we learned that microorganismes use the polymer (PHB) of a very simple chiral molecule, (R)-3-hydroxy-butanoic acid (HB), as storage material. We found out that several companies had developed, during the oil crisis of the seventies, fermentations to produce the (biodegradable) polymer PHB from renewable sources. We obtained a supply of PHB from the British company ICI, depolymerized it, and used the monomer as a cheap starting material for syntheses.[30] Over the years, we became more and more interested in the role **PHB** plays in biology:[31] R. N. Reusch has detected low-molecular-weight PHB *(ca.* 150 RB units) in numerous organisms; in a collaborative effort with her we have proved unambiguously that the complex of PHB with calcium polyphosphate isolated from *E. coli* forms Ca-specific ion channels through phospholipid bilayers (of which cell walls consist).[32] In order to understand the properties of PHB we synthesized linear and cyclic oligomers (ORB) and complexes with sodium, potassium and barium which could be characterized by single-crystal X-ray analysis. With the resulting structural data we could model conformations of the polymer (Scheme 8)[33] and propose possible structures of the ion-conducting pores and channels formed by PHB and ORBs when embedded in phospholipid bilayers,[32,34] see Scheme 9.

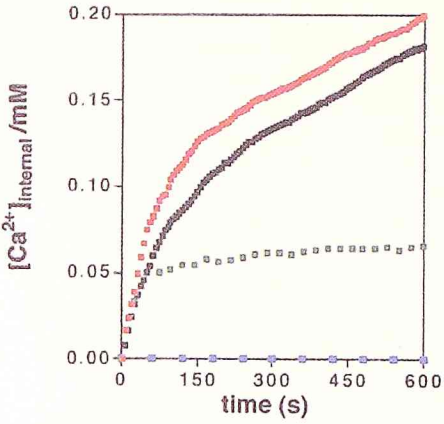
Our newest area of research has actually evolved from the work on PRB. Upon inspection of the 3_1 helix model in Scheme 8, I noticed that C=O oxygens on HB unit n and oxygens in the chain on HB unit n+2 are in close proximity, so that replacement of the chain oxygens by NH groups should lead to hydrogen-bond formation. To our surprise, nobody had actually determined the structure of an oligomer from 3-amino-acids (polymers had been made and were named NYLON-3, but turned out to have poor material properties). We synthesized a very simple β-hexapeptide in which each amino acid had been homologated (a CH_2 group inserted): H-[-β^3-HVal-β^3-HAla-β^3-HLeu-]$_2$-OH. A 2D-NMR investigation revealed that the molecule has indeed a (left-handed) 3_1-helical structure of 5Å pitch, containing 14-membered hydrogen-bonded rings, in methanol solution. In the short period since our first paper appeared[35] in 1996 and the beginning of 1999 three different helices, a parallel pleated sheet, hair-pin turns, and meander-type secondary structures of β-peptides have been identified,[36,37] see the examples in Scheme 10. Thus, there is not less structure and order in β-peptides, as predicted by those knowledgable in the field of "normal" oligo- and polypeptides, but rather more structural variety. Also, these secondary structures are much more stable than those formed by α-peptides: the helical stretches in proteins are usually built of 15 -20 amino-acid residues, while the helices of β-peptides in solution have been discovered with chain lengths of only 6 residues.[38] Furthermore, β-peptides turn out to be stable to the most vigorous mammalian peptidases, such as pepsin, pronase or the 20 S proteasome.[35,39] Thus, it is conceivable that β-peptides with appropriately located functionalized side chains can be used as metabolically stable drugs.[40] As we learn about all the secondary structures of β-peptides, we will be in a position to devise more complex, large, functional derivatives (β-proteins, β-enzymes).



Hexamer Heptamer Octamer



Scheme 8. *Structures of Oligomers and Polymers of (R)-3-Hydroxybutanoic Acid (HE) and of the Eiomacromolecule PHA.* Poly(3-hydroxyalkanoates) are ubiquitous in nature, forming microbial storage materials and being part of cellular transmembrane transport systems. Our chemical studies have led to structural information about cyclic and linear oligo-HB and to models of a 21 and a 31 helix shown here.

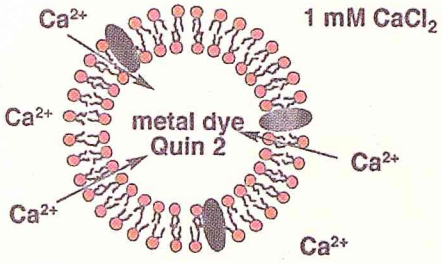


calcimycin/POPC 1 : 1000

HB-32mer/POPC 1 : 430

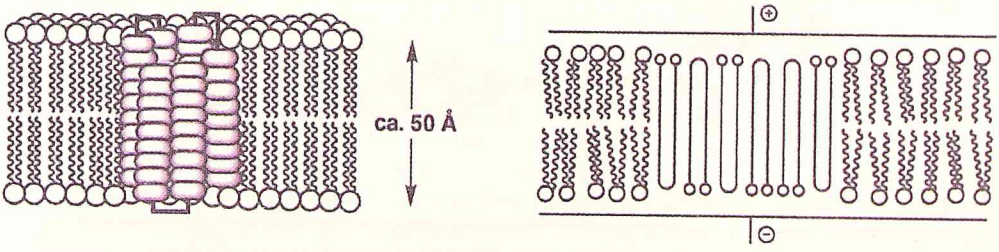
addition of 1 mM $LaCl_3$ to 32mer incorporating vesicles after 1 min

control without ionophore

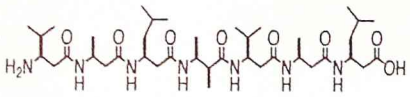


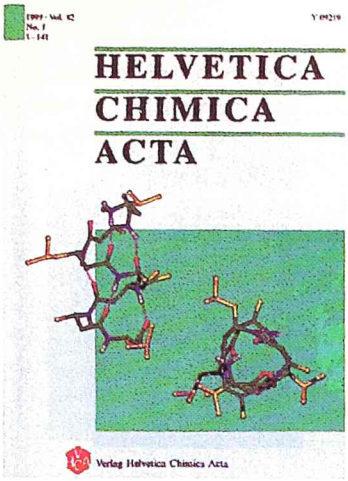
HB-Oligomer	Ca-Transport Activity
n = 8	no
n = 16	-
n = 32	yes
n = 64	yes

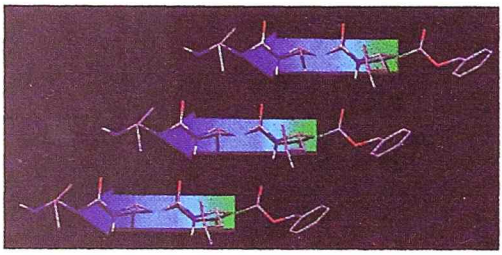
2.4 Ca^{2+} per sec per 3 HB 32mer	CARRIER MECHANISM

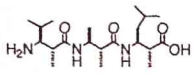


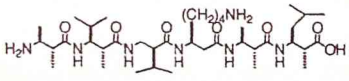
Scheme 9. *Liposomes with Incorporated Hydroxybutyrate (HB) 32mer Become Permeable for Ca^{2+} Ions, with Three Molecules forming a Pore.* Top: a fluorescence label on oligo-HB and a Ca-specific indicator entrapped in artificial vesicles allowed for determination of the kinetic parameters of Ca transport through phospholipid bilayers, and for proposal of a concentration-driven pore or carrier model (bottom left). Patch-clamp experiments, on the other hand, revealed another mode of action of PHB (an ion channel in a planar lipid bilayer) under voltage-driven conditions (bottom right).

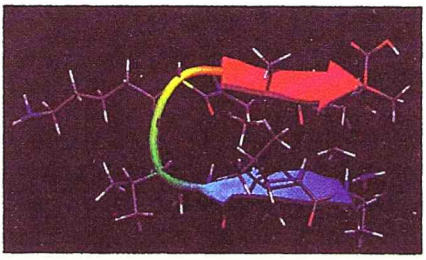






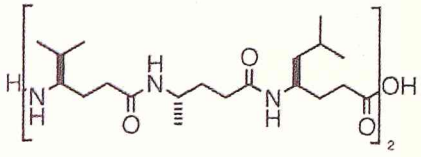


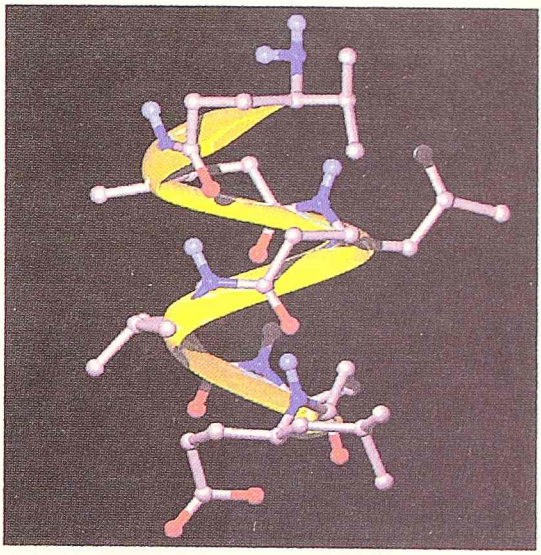




Scheme 10. *Secondary Structures of ,8-Peptides, the Homologs of the Natural a-Peptides.* A larger variety of more stable secondary structures is formed by p-peptides, as compared to a-peptides (including proteins and enzymes). Thus, helices, turns, hairpins, parallel and antiparallel pleated sheets, tube like stacking, as well as meandering structures have so far been identified. Shown here are a 31 or 314 helix (top), a parallel sheet (center), and a hairpin (bottom). Several additional structures (suggested by CD spectroscopic investigations) wait to be discovered.

We had already a first glance at the doubly homologated α-peptides, *i.e.* **y-peptides** consisting of γ^4-amino acids with proteinaceous side chains (Scheme 11), to find that they too form helices[41] which are probably even more stable than those of the β-peptides.[42]





Scheme 11. *Helical Secondary Structure of a γ-Hexapeptide Built .from the Doubly Homologated (S)-a-Amino Acids Valine, Alanine, and Leucine.* The γ-peptide forms a right-handed 2.6_{14} helix of 5Å pitch, which appears to be even more stable than the helix formed by the corresponding β-peptide.

If a common theme of my 40 years of research needs to be defined, i t will be *reactivity, stereoselectivity, structure, and mechanism in organic chemistry.* Our journey into chemistry, the science of the matter from which our uni verse is built, has been and still is exciting, and it creates more q u e s - tions as we go along. Thus, I should like to end with a quotation of a definition by the late *Rudolf Criegee,* my great teacher:

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1999 winners meet HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation
Prior to the official awards ceremony.

L to R: Professor Stephen Townley Holgate, Professor Said Abd Al-Salam Allouche, Professor Royoji Noyori, HRH Prince Salman ibn Abd Al-Aziz, Mr. Juma Al-Majid Abd Allah, HRH Prince Sultan ibn Abd Al-Aziz, Shaikh Muhammad Ibrahim Shaqra (instead of Shaikh Muhammad Nasir Ad-Din Al-Albani), Professor Patrick G. Holt, Professor Makarim Ahmad Al-Ghamri, Profesor Dieter Seebach.

WINNER OF THE 2000
KING FAISAL INTERNATIONAL PRIZE
FOR MEDICINE

PROFESSOR CYNTHIA J. KENYON

Winner of the 2000 King Faisal International Prize for Medicine

Photo: Professor Cynthia J. Kenyon receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

Cynthia Kenyon was born in 1954, in Chicago, where her father, Dr. James Kenyon was a graduate student at the University of Chicago. Her parents grew up in a beautiful area of Connecticut and nearby New York, and Cynthia developed a great love of the outdoors, spending her summers there in the country. When she was ten, her family moved to Georgia, where her father joined the Geography faculty of the University of Georgia. Her mother, too, worked at the university, as an administrator in the Physics Department. Cynthia had a happy childhood. She grew up playing the French Horn, writing poetry, reading the classics and exploring the nearby forests. She loved solving puzzles and thinking in general, but did not decide to become a scientist until she was in college. One day, when she was trying to decide what to do with her life, her mother gave her a copy of James Watson's book "The Molecular Biology of the Gene". She was fascinated by the logical nature of gene regulation, and decided then and there to study molecular biology.

Cynthia had a great love of learning, and was chosen as class valedictorian at the University of Georgia. She then went to graduate school at MIT, where she joined the laboratory of Professor Graham Walker. There she studied the response of bacteria to DNA damaging agents. At the time, it was known that these treatments could cause changes in bacterial cells; for example, their growth became filamentous, they exhibited higher DNA repair capacity, and latent bacterial viruses were triggered to replicate. Around that time, a new bacterial virus was modified that carried the beta galactosidase gene but no promoter sequence capable of driving its expression. This virus had been used to study the expression of specific genes in living cells. Cynthia realized that this virus could allow one to look for cellular genes whose expression was triggered by DNA damaging agents. Using this tool, she identified a set of genes whose expression was triggered by DNA damage. This was the first "enhancer-trap" experiment to be carried out in any organism, and it showed for the first time that DNA damage can increase the expression of a wide variety of cellular genes. By spending a year with her colleague Roger Brent in the laboratory of Mark Ptashne at Harvard, Cynthia was able to show how these genes were regulated at the molecular level. Cynthia went on to show that these genes included some that function in DNA excision repair pathways, thus demonstrating that cells have a system that up-regulates the expression of DNA repair genes under times of stress. An inducible DNA-damage response system is now known to play an important role in the regulation of oncogenesis in humans.

During her graduate work, Cynthia became interested in the question of how individual cells in an animal are instructed to express certain subsets of genes, and how this information is distributed to cells in time and space. To address these questions, she turned to the small nematode worm, *Caenorhabditis elegans.* She went to the laboratory of Dr. Sydney Brenner at the Medical Research Council in Cambridge, England, to study developmental biology. Cynthia loved living in England, both because of the beauty of the countryside and the rich intellectual culture she found

there. She especially liked going to operas and plays in London, and walking on the footpaths through the meadows of Cambridge. In the lab, she began to study an interesting developmental control gene called *mab-5*. During the course of her studies in England, which were continued in her lab at the University of California, San Francisco, she discovered that *mab-5* was a conserved homeotic (Hox) gene that gave a specific body region of the nematode its identity. These studies eventually led to her discovery (with important contributions from other labs) that body patterning in the nematode *C. elegans* is carried out by a complex of Hox genes that is very similar to the system of Hox genes that patterns the bodies of higher organisms. This was important for two reasons. First, these genes were thought to be involved primarily in the patterning of segmented animals. Her findings indicated that they affected both segmented and non-segmented animals; and thus presumably all metazoans. Thus her studies indicated that this patterning system was much more general and fundamental than been appreciated previously. Second, these findings indicated that the mechanisms that generated pattern along the body axis were much more ancient than had been thought previously. It indicated that the precursor to nematodes, insects, and vertebrates must have had a highly developed body plan that was patterned by Hox gene activities. These studies, and similar findings from other labs, have dramatically changed our appreciation of the universality and conservation of fundamental biological principles. This experience played a prominent role in motivating Cynthia's more recent studies of aging. This is because her understanding of development led her to predict that the aging process, like development, would be highly regulated by mechanisms that are conserved in evolution. So far, her studies (with important contributions from others) have shown that aging is, in fact, subject to an elaborate mode of regulation, at least in *C. elegans*. Aging in *C. elegans* is regulated by a complex and multifaceted insulin-IGF-1-like hormone system with conserved vertebrate homologs. Her laboratory has shown that signals from both the reproductive system and the olfactory system regulate aging in this animal by modulating the activity of this conserved hormone system. Cynthia is now beginning to look for conserved aging mechanisms in mice. Time will tell whether the mechanisms that regulate the aging of this small animal are conserved.

Cynthia is now the Herbert Boyer Distinguished Professor of Biochemistry and Biophysics at the University of California, San Francisco, a member of the American Academy of Arts and Sciences, and an Ellison Foundation scholar. Her pioneering studies on aging played a key role in initiating the modern molecular analysis of aging in model organisms, a rapidly growing, exciting and productive research field. She lives in a lovely cottage in San Francisco, where she spends her free time tending her rose garden, riding her bicycle, and talking long walks on the beach.

REGULATION OF AGING IN THE NEMATODE *Caenorhabditis elegans*

Cynthia J. Kenyon

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Many people consider aging to be an inevitable, passive, process caused by the gradual corrosion of cellular components over time. The hourglass runs, and then it stops. For some years, I have felt that this view might be too simplistic, and that the aging process might be subject to regulation. My thoughts were shaped by my study of development. I remember that when the field of developmental biology was young, many people were pessimistic about the prospects for progress. In particular, many predicted that the genes that control development would also control cell physiology and metabolism. Therefore, one would not be able to identify many developmental genes by looking for developmental mutations, since these mutations would kill the embryo for other reasons. In contrast, development turned out to be controlled by a system of spatially-localized regulators that behaved more logically than anyone had predicted. Many of these regulators were dedicated to the process of development after all, and their functions were readily inferred from mutant phenotypes. From this, and other predictions (for example, that DNA would play only a structural role in the cell) I came to believe that there is a tendency among scientists to underestimate the intelligence of biology.

My thoughts about aging were also influenced by our growing understanding of the evolution of developmental mechanisms. Before we knew much about development, evolutionary biologists tended to believe that the evolution of new body structures required many mutations, each advancing the new form by a tiny increment. However, the study of development showed that evolution could be driven by changes in regulatory genes, and that a single mutation could give rise to a whole new structure. For example, a mutation that caused a regulatory gene to be expressed in a new place could turn a pair of antennae into legs. In fact, evolution may have selected for regulators dedicated to the processes of development and pattern formation, because mutations affecting these types of regulators could produce new body forms without compromising cell survival.

In my view, the state of the aging field when we entered it was similar to the state of the field of developmental biology several decades ago. The molecular analysis of aging was considered by many to be uninteresting, since aging amounted to no more than the passive degeneration of cellular components. Nevertheless, it seemed clear to me that genes must determine the rate of aging, because different species can have very different lifespans. A mouse lives two years while a bat lives fifty. A possum lives three years, and a parrot, ninety. Since all these animals are thought to have evolved

from a common precursor, the diversity of lifespans we see now presumably arose from changes in genes that influence aging. Many evolutionary biologists felt (and still feel) that changes in lifespan were probably caused by many low-impact mutations, especially mutations that prevent genes from functioning properly when the animal is too old to reproduce, or when it is already likely to have died an accidental death. This view tends to make one pessimistic about the prospects for progress in aging research. In contrast, in my opinion, it would make sense for evolution to have created a system that actively regulates the aging process. First, everything else in biology appears to be under active regulation, and aging seems likely to be an important process since all animals age. Second, a system dedicated to the regulation of aging should be able to evolve easily, since single-gene mutations could change the rate of aging dramatically without interfering with other important biological processes. If a change in lifespan could increase the fitness of a species, then a group of animals with an "evolvable" regulatory system should have a competitive advantage when environmental conditions change. Thus, in thinking about these things, I had come to favor the hypothesis that aging is controlled by a more interesting and logical mechanism than many people expected. As I continued to study development, I became more and more obsessed by the desire to test this hypothesis.

We decided to look for genes that regulate aging in the same way we and others had been studying development: by isolating mutations that change lifespan. The nematode *C. elegans* is an excellent experimental organism for the study of aging because it has a short (2-3 week) lifespan and because one can use the techniques of classical and molecular genetics to identify the relevant genes. We knew it should be possible to isolate long-lived mutants, because a long-lived mutant called *age-1* had been known to exist for many years. Early in our study, we had the good fortune to find a long-lived mutant, which altered a gene called *daf-2*(1). Mutations in this gene had been known to affect a process called dauer formation, which is a growth-arrested larval stage that newly-hatched animals enter when food is limiting. Animals in which the level of *daf-2* gene activity is greatly reduced enter the dauer stage even if food is present. We discovered that animals containing weak mutations in the *daf-2* gene grew to the adult state like normal well-fed animals, but then remained youthful for much longer than normal and lived more than twice as long. These long-lived animals were healthy, active and fertile. The fact that changing a single gene could change the aging process so dramatically argued that the aging process, like most processes in biology, is regulated after all. Aging doesn't "just happen".

When we discovered that *daf-2* regulates aging, the gene was already being cloned in the laboratory of Gary Ruvkun, who had been studying the process of dauer formation. The gene turned out to encode a hormone receptor (2). This was a very informative finding, because it indicated that aging is controlled hormonally. In principle, hormonal regulation provides a simple way for an animal to coordinate the aging rates of different tissues, and it suggests ways for lifespan to be changed by single-gene mutations during evolution. It also fits nicely with our knowledge of other age-specific process, such as puberty and menopause, which are also controlled hormonally. Particularly tantalizing is the fact that we ourselves have hormone receptors that resemble the DAF-2 receptor; namely, the insulin, IGF-1, and insulin-related receptors. In a lovely series of papers, the Ruvkun lab went on to show DAF-2 regulates lifespan by activating a PI3-kinase signaling pathway much like the pathways regulated by

insulin and IGF-1 in humans (1, 3-5). We and they showed that the DAF-2 pathway appears to affect lifespan by down-regulating the activity of a conserved transcriptional regulator called DAF-16 (1,6,7). The striking conservation of this pathway raises the possibility that a branch of the complex insulin/IGF-1 hormone system controls the aging process in humans. Many biological processes are known to be highly conserved at the molecular level between *C. elegans* and humans, so there is reason to think that aging mechanisms, too, might be conserved.

In principle, the DAF-2 pathway could function within each cell to control the aging of that cell. Alternatively, the pathway could cause cells to secrete a second signal or hormone, which, in turn, would regulate the aging of individual cells. We found that if we made genetic mosaic animals in which only a subset of cells had the long-lived *daf-2* genotype, the whole animal lived longer than normal (8). Thus the DAF-2 acts to regulate the production of a second, downstream signal that more directly regulates the aging of individual cells. DAF-2 is part of a hormonal signaling cascade. Many lineages in the animal turned out to have *daf-2* activity, suggesting that *daf-2* acts in many cells to control the production of the downstream hormone. What this second hormone is, and how it affects the lifespan of individual cells, is still a mystery. Interestingly, these long-lived mutants are resistant to many forms of stress, including high temperature and agents that cause oxidative damage (9, 10). Long-lived mutants have now been isolated in Drosophila and mice, and these mutants are also stress resistant (11, 12). So are mice and rats whose lifespans have been extended by caloric restriction. Any correlation as robust as this one has a reasonable chance of being causal in nature. In other words, it is possible that these animals are long lived because they are resistant to oxidative and other stresses that normally lead to aging. This is an attractive hypothesis, but it remains to be proven.

Recently we discovered that the aging process is regulated by signals from two very different tissues in the animal. One of these is the olfactory system (13). *C. elegans* can smell and taste many different soluble and volatile compounds, which it perceives using sensory neurons in its head. A number of different mutations interfere, quite specifically, with sensory perception, either by disrupting the structure of the ciliated endings of the sensory neurons or by blocking sensory signal transduction pathways. We discovered that these sensory mutants are long lived. Likewise, if we killed the cells that form the nostrils with a laser microbeam, the animals also lived longer. These sensory mutants feed normally, and they have normal rates of development and fertility. Therefore we don't think it's likely that these worms live longer because of changes in feeding behavior, activity, or fertility. Instead, we favor the hypothesis that they live longer because of a direct influence of sensory perception on lifespan. We suspect that sensory neurons regulate the production of a hormone that affects lifespan, presumably in response to an environmental signal such as food or a pheromone. To ask whether sensory perception might regulate an insulin/IGF-1-like hormone that binds to the DAF-2 receptor, we asked what effect sensory deprivation would have on *daf-2* and *daf-16* mutants. We found that the sensory mutations had little or no effect on the lifespans of these mutants, consistent with the interpretation that sensory perception acts, at least in part, through the DAF-2/DAF-16 hormone system. A simple model would be that an environmental signal triggers release of an insulin/IGF-1-like hormone that binds to the DAF-2 receptor and accelerates the aging process. When sensory perception is prevented (or, in nature, when the

environmental signal is absent), the hormone is not released, and the level of DAF-2 activity is decreased. This extends youthfulness and lifespan.

We also found that the reproductive system, too, regulates aging (14). When we killed the germ cells, the animals lived about 60% longer than normal. One might imagine that killing the germ cells extends lifespan by preventing the animal from having progeny. However, this is not the case because removing the entire reproductive system (the germ cells as well as surrounding somatic gonadal tissues) has no effect on lifespan. Instead it appears that the germ cells produce a signal that affects lifespan; specifically, a signal that accelerates the rate of aging. This germline signal appears to act independently of *daf-2,* because if we kill the germ cells in *daf-2(-)* mutants, then they live four times as long as normal! This enormous lifespan extension is especially impressive because these animals appear relatively youthful even when they are several months old. Our studies indicate that the somatic gonad also produces a lifespan signal, one that counterbalances the germline signal and extends lifespan. Genetic experiments suggest that this somatic signal is, or regulates, an insulin/IGF-1-like hormone that acts by binding to the DAF-2 receptor. In contrast, the germline signal is not likely to act through DAF-2, but it does act through the DAF-16 transcriptional regulator. The fact that signals from the reproductive system regulate aging is thought provoking. A system like this could, in principle, coordinate an animal's schedule of reproduction with its lifespan. For example, if something were to delay the maturation of the germline, then the animal would age more slowly. This strategy would ensure that the animal remained youthful enough to bear progeny when the germline reached maturity.

Together, these studies show that aging in *C. elegans* is controlled by a surprisingly elaborate and sophisticated endocrine system. The system involves inputs from the two tissues that would seem to be particularly important to the animal in nature: its sensory system, which monitors environmental conditions like food and population density, and its reproductive system, which ensures the survival of the species over time. Both of these systems appear to regulate the aging process by affecting components of the insulin/IGF-1 signaling system. Thus this pathway may integrate lifespan signals from different tissues in order to establish the rate of aging of the animal. Our studies suggest that at least four different hormones are involved in this system: one regulated by sensory neurons, one regulated by the somatic gonad, one by the germ cells, and one by DAF-2 activity. Two of these, the somatic gonad and sensory signals, are likely to be insulin/IGF-1 like hormones. Personally, I am amazed by the power and complexity of this endocrine system. Clearly, aging is regulated in an interesting way after all. It is difficult for me to imagine that such an elaborate system evolved for nematodes alone, especially given that so many other aspects of nematode biology are highly conserved. To me, it seems more likely that a similar system regulates the lifespans of higher organisms, possibly including humans. If so, someday we may be able to use this information to improve the quality of old age in humans. This would be a wonderful accomplishment. It is my goal.

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Winners Of The 2000
King Faisal International Prize
For Science

PROFESSOR EDWARD O. WILSON

Co-Winner of the 2000 King Faisal International Prize for Science

Photo: Professor Edward O. Wilson receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

Edward O. Wilson is Pellegrino University Research Professor at Harvard University, one of fifteen university-wide professors at the university. He is also Honorary Curator in Entomology at Harvard's Museum of Comparative Zoology

Professor Wilson was born in the southern American city of Birmingham, Alabama, on June 10, 1929. Moving frequently with his family, he grew up spending variable periods in Alabama, Florida, Georgia, and Washington, D.C. He attended the University of Alabama, where he received a bachelor's and Master's degree in 1949 and 1950. He then moved to Harvard University, where he earned the Ph.D. in 1955. Following an additional postdoctoral year in Harvard's Society of Fellows, he joined the Harvard faculty, where he has served ever since.

From an early age, even prior to attending university, Wilson developed a passionate interest in natural history and especially the study of ants. In his twenties he worked widely in the field in the United States, tropical America, the South Pacific, Australia, and Sri Lanka. This research resulted in a spate of published reports on the systematics and ecology of ants, and laid the groundwork for future work in the basic principles of evolutionary biology. One product was the development, with William L. Brown, of the concept of character displacement, an important process in species formation and the assembly of biotic communities. Another was the demonstration of the logarithmic species-area relation in ants, and the concept of species equilibrium in these insects. A third was the formulation of the taxon cycle, now recognized as a widespread evolutionary phenomenon. In the cycle species spread through ecologically marginal habitats and then split and diversify as they adapt to central, species-rich environments; finally, some of the species may re-adapt to marginal habitats and disperse readily again.

Working off species-area curves and the idea of species equilibrium, Wilson joined Robert H. MacArthur in the early 1960s to develop the general theory of island biogeography. In it, the number of species on islands and other discrete ecosystems is postulated to approach a constant level as the immigration rate increases and the extinction rate decreases. The time curves of both processes depend in a predictable manner on the area of the island and its distance from other continents and other islands. The extinction rate depends on demographic properties that vary with population size, hence island area, as well as the number of similar species simultaneously present. These interlocking models had a profound effect on general biogeography and, through their focus on community formation, on general ecology as well. They were further incorporated as central concepts in the emerging discipline of conservation biology. The basic ideas were first published in an article in 1963, and developed fully in *The Theory of Island Biogeography*, a monograph published in 1967. The basic tenets have stood up well over 30 years of empirical testing.

During the same period, and on into the 1970s, Wilson also initiated the exploration of chemical communication in ants. He was the first to discover an exocrine glandular source of a pheromone used in complex social organization: the Dufour's gland as the origin of trail and excitant substances in fire ants. He then extended this work to estimate the number of such signals (10-20) employed by a typical ant species in the organization of a colony. The chemists with whom he collaborated were among the first to use gas chromatography-mass spectrometer microanalysis to identify pheromones at the microgram level, an advance that accelerated research on pheromonal communication in the social insects in the 1960s and beyond.

In the 1960s also it became apparent to Wilson that several disciplines of evolutionary biology still lingering in a primarily descriptive and disorganized condition might be integrated on a foundation of the newly emerged discipline of population biology. One achievement in the realization of this concept was the theory of island biogeography, just noted. Another, one that was to consume the middle years of Wilson's career, was the theory of social behavior. In *The Insect Societies* (1971) he brought together most of the existing knowledge of the social insects (ants, bees, wasps, and termites) into a conceptual framework of population biology combined with pheromone and caste research and the newly created kin selection theory of William D. Hamilton. At that time he established a modern version of sociobiology, defined as the systematic study of the biological basis of all forms of social behavior. Within the framework of sociobiology, Wilson suggested, we can discern the common principles that explain the origin of sociality in animals otherwise as different as termites and chimpanzees.

In 1975 Wilson extended the reach of the subject thus predicated in order to include vertebrates. The more comprehensive treatise created was *Sociobiology: The New Synthesis* (1975). This work was very favorably received, and it is generally credited with having helped revolutionize the study of animal behavior by placing social organization on a solid evolutionary basis. In 1989 it was voted by officers and fellows of the Animal Behavior Society as the most important book on animal behavior of all time.

Because Wilson included *Homo sapiens* (a vertebrate species), *Sociobiology: The New Synthesis* was also a focus of controversy, originating from intense criticism by Marxist thinkers and social scientists devoted to the idea of the exclusive primacy of culture and history in human affairs. With the passage of time, however, the objections have largely faded away, as the strong influence of biology and its complex interaction with learning and culture have become more obvious.

In 1998, incorporating the more advanced knowledge now available from sociobiology, genetics, neuroscience, and anthropology, Wilson published *Consilience: The Unity of Knowledge*, pointing to the growing union of biology, the social sciences, and humanities, and the major implications of such a union for the future of education and social policy.

Since the 1970s Wilson has become increasingly involved in the global conservation movement, entailing both basic research and practice in the field. In 1988, he edited *Biodiversity*, which introduced the word (short for biological diversity), and in 1992 he

synthesized the basic principles of biodiversity research and conservation practice in *The Diversity of Life* (1992).

Wilson's life work has been given abundant recognition. He has been elected to many academies, including the National Academy of Science, the Royal Society, the Leopoldina (German Academy of Sciences), and the Russian Academy of Natural Sciences. His awards include the U.S. National Medal of Science, International Prize for Biology (Japan), Crafoord Prize of the Royal Swedish Academy, Nonino Prize (Italy), Gold Medal of the Worldwide Fund for Nature, and Benjamin Franklin Medal of the American Philosophical Society. For his writings he has received many literary awards, including two Pulitzer Prizes (1979, 1991), In pursuit of his conservation work and promotion of general higher education he serves on the Board of Directors of Conservation International, the American Museum of Natural History, and The Nature Conservancy, among others.

Today Professor Wilson lives with his wife Irene in Lexington, Massachusetts. They have one daughter, Catherine, who lives with her husband in a town nearby.

THE IMPORTANCE OF BIODIVERSITY

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The faunas and floras of the world are the life support system of humanity. The reason is that they are the cradle in which our species evolved and to which we are exquisitely adapted in body and mind. The variety of life composing the biosphere is also immense and still poorly understood. Since Carolus Linnaeus inaugurated the now-standard binomial-hierarchical classification in 1758, biologists have described and given formal names to between 1.5 and 1.8 million species. The true number is far greater, however. Estimates in recent years have ranged from 5 million to 100 million. Which of these two extremes is closer to reality depends on the magnitude of diversity in very large but still mostly unexplored groups such as bacteria, fungi, nematode worms, and insects.

Biodiversity is not spread randomly over Earth's surface. It is concentrated in certain habitats, such as the tropical rain forests, the planet's natural greenhouses, and the coral reefs, the rain forests of the sea. How biodiversity arose and came to be distributed to attain its present-day pattern remains one of the great problems of the biological sciences. In various manifestations it has held my attention throughout most of my life.

When still a student at the University of Alabama, I came to realize that natural history, the descriptive account of biodiversity, can be transformed into solid science if framed to address questions of evolution. One such question that first attracted me is biotic dominance. Which parts of the world, biologists have repeatedly asked, produced the plant and animal groups most able to spread to other parts and compete successfully there? By the late 1940s a consensus was emerging that on the land at least, the headquarters from which dominant groups originate and spread are the Old World tropics, a great swath of geography extending from equatorial Africa through the Middle East to mainland tropical Asia and present-day Indonesia.

When I set out in 1954 to explore the ant fauna of the South Pacific, I had faunal dominance as one of my key orienting concepts. I was curious to know which species in particular—as opposed to groups of species at the level of genus and family—have been pioneers of dispersal, and which traits, if any, they also possessed in common. When I returned a year later after intensive work in Australia, New Guinea, New Caledonia, and Vanuatu, I was able to piece together patterns from my database of systematics and ecology in a search for the answers. I generalized the main result as the "taxon cycle": for this part of the world, at least, species of ants originate mostly on the larger land masses of Australia and southeast Asia, and spread to the smaller land

masses of New Guinea and other Melanesian islands. The pioneers are specifically adapted to marginal environments such as savannas and river courses that serve as potential overseas launching ramps. Upon reaching the peripheral islands, they tend to evolve to colonize and diversify within the central forest environments, often replacing older native species that preceded them.

One of the patterns revealed by such studies of biotic dominance and taxon cycles was equilibrium: through evolutionary time (i.e., thousands to millions of years), as new species invade and diversify to the levels of genus and family, old groups shrink and disappear to equivalent degree. The two processes maintain at least a very rough balance in biodiversity. This phenomenon was very much on my mind when I met and began a series of conversations with the ecologist Robert H. MacArthur in 1960. At that time I showed him the area-species curves of the Pacific ants I had compiled, as well as those of vertebrates taken from the data of other authors. As the area of individual islands of an archipelagic system such as Melanesia or the West Indies increases, the number of species also increases, and logarithmically, as $S = bA^X$, where S is the number of species on a particular island, A is the area of the islands, x is a constant dependent on the archipelagos and group of organisms, and b is a fitted constant. In most cases, my own and subsequent research revealed, x usually falls between 0.15 and 0.33. Many cases are at or near 0.27, which can be translated into intuitively clear formulation as follows: a 10X increase in area results in a 2X increase in the number of species of ants, birds, or any other group of organisms chosen for observation.

MacArthur next proposed the following crossed-curve model to account for the equilibrium. During colonization of an island, and as the number of species rises, the rate at which additional species colonizes the island falls and the rate at which resident species go extinct rises. When the two curves meet, in other words extinction equals immigration, the number of species on the island (of ants, birds, or any other group) is stabilized. This principle and others were first published in a 1963 article and then explored more fully in our 1967 monograph *The Theory of Island Biogeography*. The approach we took is now a standard part of ecology and conservation biology.

With the maturing of island-biogeographic theory, I began to cast about for a means of testing it experimentally. In the mid-1960s, in collaboration with my student Daniel Simberloff (now a distinguished senior ecologist), I devised the first natural-system test of biogeography. The sites chosen were mangrove islets in the Florida Keys, south of Miami. Each was less than 20 meters in diameter. While not true ecological islands to birds, people, or butterflies, they did have that status for most insects, spiders, and other arthropods, whose breeding populations reached into the dozens, hundreds, or even thousands. Simberloff and I first censused and identified the arthropods of a small set of the islets, in the midst of thousands present in Florida Bay. We then arranged for one subset of the islets to be fumigated, thus eliminating all of the resident arthropods. We also had the remainder mock-fumigated, leaving their faunas intact as controls. Within two years the number of species in the "defaunated" islets regained the same levels present before fumigation. The species compositions were substantially different from before fumigation, and from islet to islet afterward as well, but in each case the original *number* of species was roughly the same.

The theory of island biogeography produced a warning for conservationists. Both reason and mounting evidence pointed to the need to make nature reserves as large as possible. Suppose that in the course of the clear-cutting of a forest, a country sets aside a small park to preserve the species of plants and animals that would otherwise be extinguished. We now know that even if at first some representatives of most or all the species are present in the little reserve, the number of species will decline over a period of years to about the levels expected of an island the size of the park. Such is occurring, for example, in the mammal faunas of the national parks of the United States and Canada.

All around the world, natural environments—forests, grasslands, river systems, coral reefs, and others—are being reduced at an accelerating rate. They are yielding to human populations that continue to explode, especially in the developing countries, and the efforts of people everywhere to increase their consumption and quality of life. Specialists on biodiversity are in unanimous agreement that the worldwide rate at which animal and plant species are being eliminated or doomed to early extinction is at least as high as 100X and possibly 10,000X or more the rate before modern *Homo sapiens* appeared on Earth some 500,000 years ago. If present trends of environmental conversion continue, half the world's species could be gone or on the brink of extinction by the end of the present century. We have entrained a spasm of extinction potentially as great as the one that accompanied the giant meteorite strike of 65 million years ago, wiping out the last of the dinosaurs and thus terminating the Age of Reptiles.

The reasons for avoiding this new, manmade catastrophe are multiple and compelling. Natural ecosystems renew our soils, replenish our water, and generate the very air we breathe. They do it free of charge and with greater efficiency than any agricultural or other manufactured ecosystems humans have created. The millions surviving wild species, which remain mostly unexamined and even unnamed, are a potentially endless source of new pharmaceuticals, crops, fishes, fuels, and other natural products—but only if protected and studied properly. Finally, there is a fundamental moral reason for global conservation, consilient with the tenets of the world's great religions. Who are we, scientists and theologians are now asking, to destroy a large part of life on this planet?

In the new century, humanity faces two interlocking challenges that arise from our own biological nature. While stabilizing our own population, we must find the way to raise the quality of life of people everywhere to a higher level while simultaneously protecting the rest of the biosphere. To achieve both will require all of the best of science and technology we can bring to bear, guided by a global ethic considers the creation and the rights of future generations as inviolable.

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DR. J. CRAIG VENTER

Co-Winner of the 2000 King Faisal International Prize for Science

Photo: Dr. J. Craig Venter receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier and Minister of Defense and Aviation

SYNOPSIS OF ACHIEVEMENTS

John Craig Venter was born on October 14, 1946 in Salt Lake City in Utah. After completing high school in San Fransisco, he moved to the beaches of Southern California where he spent his time surfing and sailing. In 1967, he joined the Navy as a medical corpsman in the Vietnam War. Stationed at the Naval Hospital in Danang, and serving as the senior corpsman in the emergency room during the Tet offensive, he spent many days working round the clock to help thousands of injured soldiers. That experience taught him first hand how tenuous our hold on life can be. He also wondered "why it was that some of us live through devastating bodily trauma whereas others die from seemingly small wounds." Venter's war-experience dramatically altered his life and gave him his insatiable quest for an understanding of life at its most basic level. The Vietnam experience also impressed on him the idea that time is precious and that we should use every single day to the fullest.

After the War, Venter decided to go to college. Within merely six years, he completed his B.A. in Biochemistry and Ph.D. in Physiology and Biochemistry at the University of California in San Diego. He then joined the State University of New York (SUNY) as Assistant Professor of Pharmacology and Therapeutics at Buffalo Schools of Medicine and Dentistry then became Associate Professor of Biochemistry, Associate Chief Cancer Research Professor (Scientist), Adjunct Professor of Biochemical Pharmacology and Research Professor of Biochemistry at SUNY. Between 1984-1992, he also worked at the National Institutes of Health in Bethesda, Maryland where he held several positions, including: Chief of the Receptor Biochemistry Section, Chief of the Receptor Biochemistry and Molecular Biology Section and Co-Director of the Laboratory of Molecular and Cellular Neurobiology, Chief of the Laboratory of Molecular and Cellular Neurobiology and finally Director of NINDS DNA Facility and Chief, Receptor Biochemistry and Molecular Biology Section at the Director's Office.

Dr. Venter left NIH in 1992 to enter the private sector. In 1992, he co-founded The Institute for Genomic Research (TIGR) with W. Steinberg, and in 1998 he founded Celera Genomics with Perkin-Elmer. Since then, he was performing genomic sequencing and gathering genomic data at breakneck speed.

He met Clair M. Fraser in the late 1970's. They married, and Clair - a noted molecular biologist - soon became a key member of his research team, which included other distinguished scientists like Hamilton O. Smith, Mark Adams, Gene Myers and Granger Sutton.

Dr. Venter's outstanding progress in the field of genomics has rapidly established him as the world's leader in genome sequencing technology. He was the first to put high throughput automated DNA sequencing into practice, and to develop the highly efficient expressed sequence tags (ESTs) method for rapid discovery of human genes and for whole genomic random sequencing for small genomes. He was also the first to sequence the entire genome of a free-living organism, *Haemophilus influenzae*. This

landmark achievement was soon followed by sequencing of entire genomes of other organisms, including 14 complete microbial genomes in Venter's laboratory. Dr. Venter has applied the whole genome shotgun method of sequencing to larger, more complex organisms as well. A team, led by Dr. Venter, has recently sequenced the complete genome of *Drosophila melanogaster* and the entire sequence of the human genome.

TOWARDS A GENOMIC-BASED SCIENCE OF MEDICINE

J. Craig Venter

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ABSTRACT:

The power and effectiveness of science and medicine are about to be transformed in very far-reaching ways. We now know the entire genome for the fruit fly, an important model for human biology and disease. We now have at our disposal the reference DNA sequence for the entire human genome, containing roughly 3.5 billion letters of the genetic code. At the same time, the science of whole genome sequencing is fostering the computational science of bioinformatics needed to develop practical applications for biology, agriculture, and medicine. These developments will change basic science, agriculture and medicine on a worldwide basis. This prospect should stimulate the scientific and medical research communities to pursue their goals with a renewed sense of optimism and urgency. At the same time, all of us will need to maintain an appropriate sense of humility as to how much yet remains to be done.

A COMPLETE REFERENCE SEQUENCE FOR THE HUMAN GENOME

Our DNA sequence and its variation provide a special record of human history, including the fundamental unity of all human beings, and the migration of populations (1-14). We will learn how this sequence varies among populations and among individuals, including the role of such variation in the pathogenesis of important illnesses and responses to pharmaceuticals. We will localize and annotate every human gene and the regulatory elements that control the timing, tissue-site specificity and extent of gene expression. For any given physiologic process, we will have a new paradigm for addressing its evolution, its development, its function, and its mechanism. This will revitalize medicine by identifying important new targets for prevention, diagnosis, and therapy. Scientists will be able to approach issues of rational candidate drug-design and the reduction of serious side effects by using bioinformatics to analyze the relevant genes and gene-variations (polymorphisms), including the promoters and the enhancers involved. Knowledge regarding the alleles that govern the safety and efficacy of pharmaceutical agents (including comparative genomics) will make it possible to streamline the pre-clinical and clinical development of new drugs and customize interventions to the specific genotypes of patients. Medical progress will be driven more by knowledge of gene structure and function and less by empiricism and intuition. Moreover, science will be able to address the special needs of the

developing world, including malnutrition and susceptibility to diseases that should have already been vanquished.

It is important to recall that the first complete genome of any free-living organism (***Haemophilus influenzae***) was published by my team at The Institute for Genomic Research (TIGR) only 5 years ago (15). During the first 5 years after this publication, the sequences of the entire genomes of approximately 25 organisms were published (15-37), and within the very near future the number may well exceed 100. (Table1, http://www.tigr.org) What was, a few short years ago, thought to be impossible has become not merely possible but inevitable. We have now compiled the entire human genomic DNA sequence and will publish our work by the end of this year. The genome sequence will be available to the world via the Internet. I think this will be the beginning of the revolution of medicine.

WHOLE GENOME SEQUENCING

What has led us to such a breakthrough? The development of advanced automation, robotics, computer software and super computing for genome-scale DNA sequencing has proceeded at a remarkable pace. (See Figure 1 for illustrations of the genome sequence factory concept and whole-genome shotgun sequencing.) With the successful sequencing of the ***H. influenzae*** genome in its entirety by TIGR, it became clear that the DNA of entire complex organisms could be accurately and rapidly sequenced by using a whole genome "shotgun" sequencing strategy (14).

In this strategy, random DNA-fragment-libraries are prepared following mechanical or sonic shearing of entire genomic DNA and inserted in suitable vector systems. The ends of a tens of thousands of tens of millions randomly selected fragments are sequenced from both insert ends until every part of the genome has been sequenced several times on average. For any given average sequence read-length, the number of end sequences needed can be determined by standard statistical principles. The sequences are then computationally "re-assembled" to provide the complete genome. For higher organisms, which contain one set of chromosomes from the mother and one set of chromosomes from the father, this approach yields an important dividend: Points of common DNA variation such as single nucleotide polymorphisms become evident.

This overall strategy coupled with the advent of a completely automated DNA sequencing machine, the new ABI Prism 3700 DNA Analyzer (manufactured by PE Biosystems, PE Corp.), made it possible for a single center, such as the one I lead, to undertake the determination of the reference sequence of the human genome. Indeed, we have completed sequencing the genome of our first human volunteer. The successful application of our approach creates the opportunity where every organism of pharmacologic or toxicologic interest is now a candidate for whole genome sequencing. The science and supporting technology are here now.

THE CHALLENGE OF MICROBIAL PATHOGENS

Microbial pathogens (e.g., tuberculosis, cholera, and malaria) are a source of great suffering and death in many developing countries. Moreover, even in nations with advanced health-care technologies and mature research-based pharmaceutical industries, the emergence of multi-drug resistant pathogens is a serious problem. Indeed, some have argued that we are not too far removed from a return to the prepenicillin era in the fight against infectious disease. The problem for research pharmacologists is formidable and getting worse. The evolving field of genomic sequencing allows unique opportunities for understanding microbial pathogenesis and control by having simultaneously at hand the genomes of the pathogen and host.

Knowing the complete genome of microbial pathogens has opened up exciting opportunities to develop novel pharmaceuticals and biologics. We will know how many genes are contained in each pathogen, where they are located within that pathogen's genome, and when two or more similar genes (paralogs) exist in a single microbial genome, thereby creating the potential to confound the research pharmacologist's search for an Achilles heel. By simultaneously analyzing the microbial genome and the host genome, it will become possible to define which genes are critical for microbial survival and which are optional, why a given pathogen is virulent in the context of a specific host, how and when toxic cytokines are activated within a host, whether a given pathogen has evolved proteins with molecular mimicry capable of frustrating host immunity or inducing autoimmunity, and how a pathogen (e.g., the tubercle bacillus) is able to survive in a state of latency or dormancy, impervious to the host's immune system. The sum total of this information will make it possible to define vaccines that induce specific and effective immunity against the pathogen while minimizing untoward or toxic side effects in the host.

Recently, the team I lead at the Institute for Genomic Research provided the complete 2,272,351-base pair genome of ***Neisseria meningitides*** strain MC58 (38). This bacterium contains more genes that undergo variation than any other microbial pathogen studied to date. Since ***N. meningitides*** is a major cause of bacterial septicemia and lethal meningitis, this genomic knowledge should provide a foundation for new approaches to deal with the sequence variation of surface-exposed proteins (and the cross-reactivity of the serogroup B capsular polysaccharide with normal human tissue). We have used our whole-genome knowledge to identify antigens that are 1.) surface-exposed, 2.) conserved across many strains, and 3.) effective in inducing bactericidal antibodies in murine models of human immune responses (39).

Malaria provides a special model for the challenges and research opportunities, and Wahlgren (40) has provided an elegant perspective on this topic. ***Falciparum malaria*** is a leading killer in the African countryside, and multi-drug resistant forms of the disease have emerged on a wide scale. The disease is caused by a protozoan (***Plasmodium falciparum***), whose life cycle involves infecting human erythrocytes, which in turn causes a fulminant hemolytic anemia. One consequence is cerebral malaria, a process facilitated by the patient's own cytokines, which promote adhesion of malarial organisms or their detritus to the inside walls of blood vessels. The resulting cerebral ischemia is often lethal, and perhaps one million people, many of them children, die from this infectious kind of stroke every year.

The best-known genes for malarial protection are those for which resistance-alleles (nucleotide substitutions) in people in endemic regions exist in a state of balanced polymorphism. Thus, people with one copy of the S allele of the Beta subunit of hemoglobin have a selective advantage living in malaria-endemic zones compared with individuals with two wild type alleles, or with two copies of the mutant allele (in which case they would exhibit sickle cell anemia). The α- and β- thalassemias and glucose-6-phosphate dehydrogenase deficiencies are other examples of genotype polymorphisms whose evolution was driven by the selective advantage conferred on account of resistance to malaria.

The ***P. falciparum*** genome is roughly 30Mb in size and contains 14 chromosomes. Recently, after overcoming a number of theoretical and practical obstacles owing to the adenine plus thymine richness of its genome, TIGR was the first to obtain the entire DNA sequence of one malaria chromosome (chromosome 2 in ***P. falciparum*** (41)). The coupling of whole genome information from ***P. falciparum*** with whole genome information from its human host is likely to initiate an entire range of new approaches for dealing with the problem of malaria. (It is also possible that DNA sequencing of the intermediary host mosquito or a related insect genome may add still another set of strategic targets for attacking malaria.) The development of knowledge useful in turning the tide against multi-drug resistant malaria is a crucial goal for the science of whole genome sequencing.

These points provide but a small glimpse of the process that is likely in the future. Our understanding of the full genomes of various pathogens (Table 1) will enable new strategies to prevent and treat a host of important pathogens, including ***H. influenzae, Helicobacter pylori, E. coli, Mycobacterium tuburculosis, Treponema pallidum, Chlamydia trachomatis, Giardia lamblia, Pneumocystis carinii, Pseudomonas aeruginosa*** to name a few. In addition, a wealth of information elucidating how host resistance genes function will emerge. For example, in AIDS, a number of host genes are already known to govern initial susceptibility or resistance to AIDS virus infection and its subsequent clinical progression (42-45). Similar considerations apply to the ***Nramp*** gene in connection with resistance to pathogen-induced diseases such as tuberculosis in the Gambia (46,47).

DNA SEQUENCE VARIATION

We all share >99.9% of the nucleotide sequence in our genome, so it is remarkable that the extraordinary diversity of human beings is encoded by only 0.1% variation in our DNA. We are predisposed to different diseases, we respond to the environment (including exposure to pathogens) in variable ways, we metabolize pharmaceutical agents differently, we may show differences in dose-response relationships for common drugs, and we have a range of susceptibilities to adverse side effects from therapeutic agents (even when there is no discernible difference in individual pharmacokinetics or biochemical pharmacology). Despite the overwhelming similarity in sequence, there are approximately 3 million points of DNA variation between any two randomly selected individuals. An understanding of DNA variation may explain a great deal about causation, prevention, diagnosis, and treatment of diseases.

The most common form of DNA variation is single nucleotide polymorphism (SNP) (1-14; 48). Put simply, a SNP is the substitution of one purine or pyrimidine nucleotide at a given location in a strand of DNA for another purine or pyrimidine nucleotide. Such substitutions can affect gene function, or they can be neutral. Neutrality is generally inferred if a SNP does not alter protein-coding. In practice, this inference can be wrong.

SNPs may occur inside or outside of a gene. If they occur within a gene, they may reside in an exon (coding region) or intron (non-coding) region. SNPs in a coding region (sometimes called cSNPs) can either be synonymous (no amino acid altering effect) or non-synonymous (amino-acid altering). There is some level of natural selection against amino-acid altering changes (12, 13). The average person would be expected to be heterozygous for roughly 40,000 non-synonymous (amino-acid altering) alleles (12).

The information obtained from whole genome shotgun sequencing is also a very efficient method for generating information on SNPs. This information will allow scientists and doctors to understand how DNA variation has an impact on disease causation, as well as prevention, diagnosis, and treatment.

Thus, on several fronts, pharmacologists and toxicologists will be able to address issues of efficacy and safety not reflected in the traditional pharmacokinetic or pharmacodynamic profiles of drugs. Even when patients have identical pharmacokinetic profiles for a given drug, we currently have no way of knowing that there will be comparable inter-patient efficacy or safety because the science of pharmacogenetics can now only look at one part of the picture, and even that picture generally excludes important classes of therapeutics such as biologic response modifiers and monoclonal antibodies. In the future, the growing knowledge, based on the foundation of the complete human genome, will make it possible for pharmaceutical developers to select therapeutic agents according to the individual SNP profiles of the intended patient. Said another way, patients will someday get only the drugs they need, and none other. But what is certain now is that pharmacology and toxicology will become dependent on the emerging bioinformatics and computational sciences linked to genomics. Data acquisition and management across multiple disciplines will require new tools and skill-sets, necessitating changes in the curricula of pharmacology teaching centers toward much more computational orientation. It will also be necessary for new cross-relational data bases to emerge to serve the needs of pharmacologists and toxicologists in the new genomics era.

COMPARATIVE GENOMICS

The availability of whole genome sequence information in the human is important in its own right, but the full power of this knowledge requires the additional availability of whole genome sequence information from model organisms, especially ***Drosophila melanogaster*** (common fruit flies) and mice. Drosophila has been at the forefront of genetics research for nearly 80 years. This species is an important model for combining genetics, electrophysiology and molecular biology. We recently published

the entire genomic sequence for the fruit fly (49-51). A brief listing of some human disease causing genes found in the fruit fly is shown in Table 2. We now know the entire gene-set (nearly 14,000 genes) in the fruit fly. This represents a very important step for biologists across many disciplines.

In the case of vertebrate organisms, not only does homology to human genes exist, there is also something more meaningful called synteny. This means there are related genes arrayed on chromosomes common to human counterparts, in a comparable order in terms of exons and gene regulatory elements. Thus, a mouse chromosomal region with such a common history and genetic arrangement is said to be syntenic, and the relevant mouse and human genes are said to be orthologs. Synteny and the capacity to overlay complete human and mammalian genome sequences will affect gene discovery and our understanding of gene structure and function in ways without precedent. We expect the completion of other genomes with importance to pharmacology and toxicology, e.g. rat and canine genomes, not too far behind those of humans and mice. These advances will allow an integration of information from transgenic animals and gene knock- out models in far reaching ways and will stimulate novel strategies for currently intractable therapeutic problems.

Knowledge from comparative genomics may make it possible to re-think therapeutic strategies for currently untreatable disorders, including those that arise from cytogenetic abnormalities. For example, is it possible that if an appropriate intervention were made early enough, Down's syndrome (trisomy, critical region chromosome 21q22.2 - q22.3) might not inevitably lead to mental retardation? Asked another way, do the models of phenylketonuria and congenital hypothyroidism apply?. Is there a way of testing whether an extra dose of a gene causes mental retardation, and could a pharmaceutical agent somehow neutralize the effects of such an extra dose if given early enough? One could note, with some justification, the futility of such hypotheticals in the absence of knowledge of the genes responsible for the disorder, and this underscores the importance of completing the human genome sequence effort quickly.

By utilizing available knowledge of synteny and comparative genomics, a novel family of protein kinases, called Dyrk, was found that represents interesting candidates for a role in this syndrome (52). Human chromosome 21 and the syntenic region of mouse chromosome 16 are known (53, 54). The gene *Dyrk1A* is located in the Down's syndrome critical region of chromosome 21. *Dyrk1A* reveals homologies with *minibrain,* a gene in Drosophila whose mutations yield reduced neuronal number and defective learning behavior. Mouse models of Down's syndrome, which involve a partial trisomy 16, have been created (55, 56). And perhaps most interesting, mice transgenic for a 180kb DNA segment derived from the human Down's syndrome critical region had defects in learning and memory (57, 58). Thus, it may soon be possible to identify both the gene(s) responsible for the most significant feature of the syndrome and in vivo systems for designing and testing interventions. These types of research opportunities will be multiplied thousands of times with the completion of the reference human genome program.

SOCIETAL RESPONSIBILITY

We now have an established science of whole genome sequencing and moreover, the sequencing of the genome of a human being is completed. It is worth discussing the limits of genomics. Understanding the human genome will change science and medicine in profound ways. It will, however, not solve or explain every important problem of the public health. Other components of society will need to express determination and commit resources for solutions. One such problem is the need to respect patient privacy. Another is racism in whatever guise, which is invariably an enemy of science. I cannot fully express how important it is for all of us to renounce any application of genomic science intended to harm others or provide a rationale for such harm. In our efforts to provide a reference sequence for the human genome, I believe there is neither "good" nor "bad" DNA, only human DNA. Every individual will have a finite number of genetic flaws in his or her genome. Our task is to use the modern tools of genomics and medical science to ameliorate these flaws or undo their consequences. There is very good reason for optimism on this front as I have tried to convey in this review. Yet many societies, including my own, have at various times embraced eugenics and other irrational genetic theories of race or ethnicity as the justification for neglect, oppression or worse. However, the embrace of these destructive philosophies is not inevitable. Opening incomparable opportunities for preventing and curing illnesses through genomic science is one way of refuting these pseudo-scientific viewpoints. I believe that various governmental and private agencies need to re-double their efforts to provide resources in the arena of ethics, education and genomic research. Furthermore, some illnesses have their roots in certain external environmental factors, for which genes may not affect outcomes in practical terms. Poverty may be viewed as one such factor. It is, therefore, important for society at large, and especially scientists, to recognize that advances in science alone, including the genome science discussed here, must be coupled with programs to address these larger societal issues. These views are congruent with the general philosophical theories of E. O. Wilson, my distinguished colleague in this award program. I know that we can meet these challenges.

Figure 1

Figure 1A

Figure 1

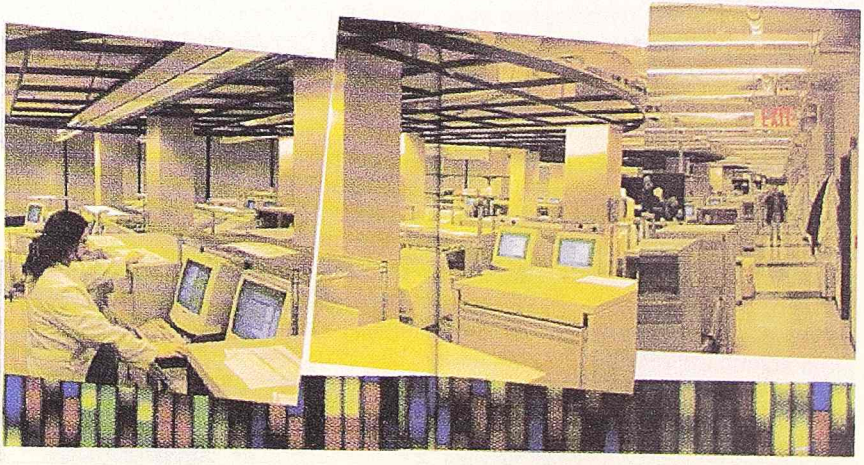


Figure 1C

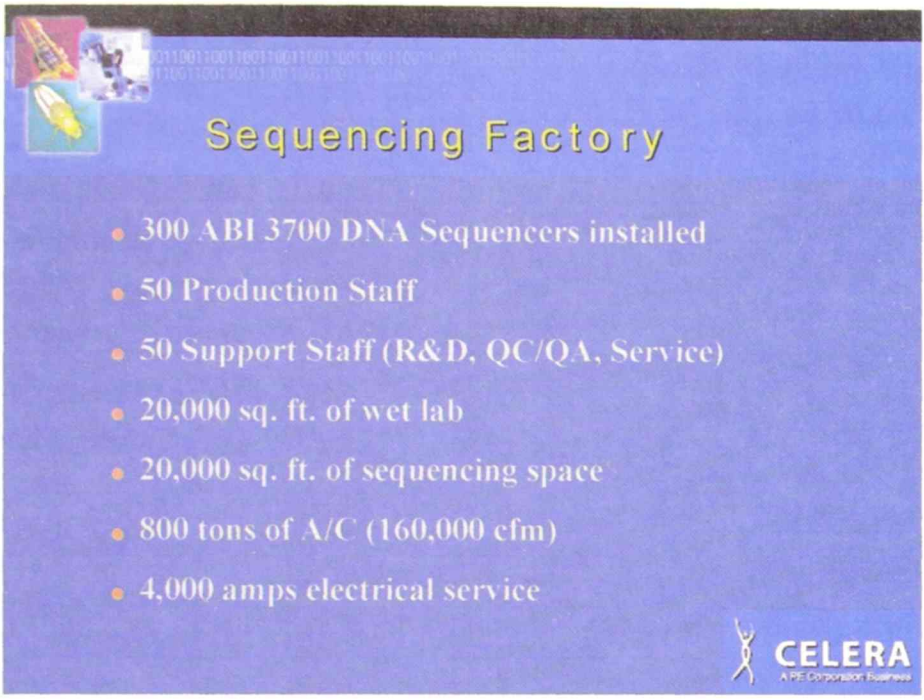


Figure 1D

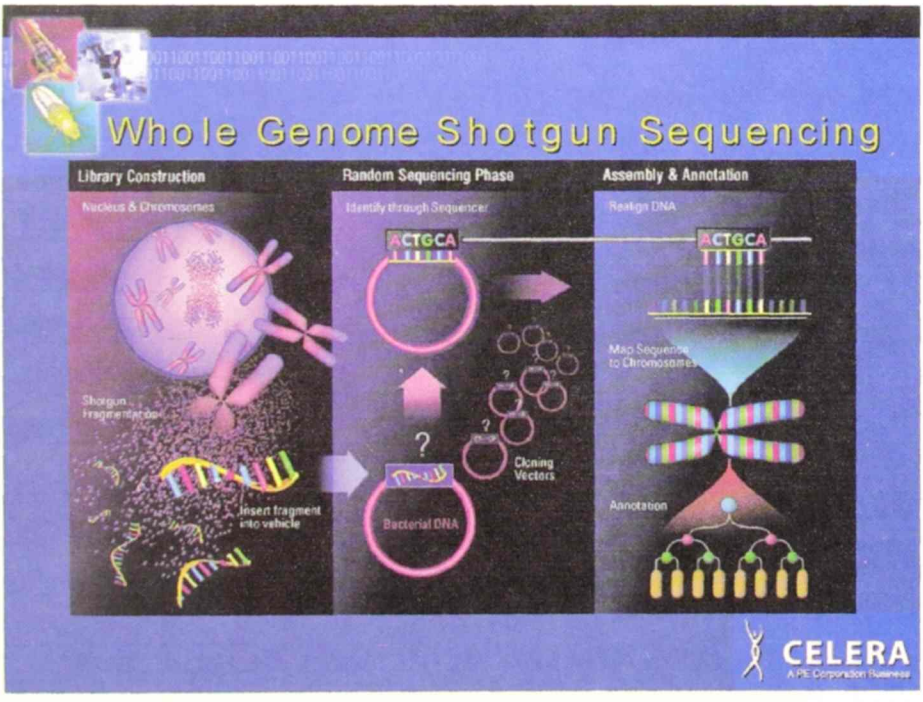


Table I

1A: Genomes & Chromosomes
(modified from the TIGR database)

Genome	Strain	Domain	Size (Mb)	Institution	Funding	Publication
Haemophilus influenzae Rd	KW20	B	1.83	TIGR	TIGR	Fleischmann *et. al., Science* **269**:496-512 (1995)
Mycoplasma genitalium	G-37	B	0.58	TIGR	DOE	Fraser *et. al., Science* **270**:397-403 (1995)
Methanococcus jannaschii	DSM 2661	A	1.66	TIGR	DOE	Bult *et. al., Science* **273**:1058-1073 (1996)
Synechocystis sp.	PCC 6803	B	3.57	Kazusa DNA Research Inst.		Kaneko *et. al., DNA Res.* **3**: 109-136 (1996)
Mycoplasma pneumoniae	M129	B	0.81	Univ. of Heidelberg	DFG	Himmelreich et. al., *Nuc. Acid Res.* **24**:4420-4449 (1996)
Saccharomyces cerevisiae	S288C	E	13	International Consortium	EC, NHGRI, Welcome Trust, McGill U., RIKEN	Goffeau et. al., *Nature* **387** (Suppl.) 5-105 (1997)
Helicobacter pylori	26695	B	1.66	TIGR	TIGR	Tomb *et. al., Nature***388**:539-547 (1997)
Escherichia coli	K-12	B	4.60	University of Wisconsin	NHGRI	Blattner *et. al., Science* **277**:1453-1474 (1997)
Methanobacterium thermoautotrophicum	delta H	A	1.75	Genome Therapeutics & Ohio State Univ.	DOE	Smith *et.al., J. Bacteriology*, **179**:7135-7155 (1997)
Bacillus subtilis	168	B	4.20	International Consortium	EC	Kunst *et.al., Nature***390**: 249-256 (1997)
Archaeoglobus fulgidus	DSM4304	A	2.18	TIGR	DOE	Klenk *et al.,Nature* **390**:364-370 (1997)
Borrelia burgdorferi	B31	B	1.44	TIGR	Mathers Foundation	Fraser *et al., Nature*, **390**: 580-586 (1997) / Casjens *et al., Mol Microbiol*, **35,/B>: 490-516 (2000)**
Aquifex aeolicus	VF5	B	1.50	Diversa	DOE , Diversa	Deckert *et al., Nature***392**:353 (1998)
Pyrococcus horikoshii	OT3	A	1.80	Biotechnology Center	NITE	Kawarabayasi *et al., DNA Research* **5**: 55-76 (1998)
Mycobacterium tuberculosis	H37Rv (lab strain)	B	4.40	Sanger Centre	Wellcome Trust	Cole *et al., Nature***393**:537 (1998)
Treponema pallidum	Nichols	B	1.14	TIGR/ Univ. Texas	NIAID	Fraser *et al., Science* **281**: 375-388 (1998)
Chlamydia trachomatis	serovar D (D/UW-3/Cx)	B	1.05	UC Berkeley & Stanford	NIAID	Stephens *et al., Science* **282**: 754-759 (1998)
Plasmodium falciparum Chr2	isolate 3D7	E	1.00	TIGR /NMRI	NIAID	Gardner *et. al., Science***282**:1126-1132 (1998)
Rickettsia prowazekii	Madrid E	B	1.10	University of Uppsala	SSF / NFR	Andersson *et al., Nature* **396**: 133-140 (1998)
Caenorhabditis elegans			100	Washington Univ & Sanger Centre		Science 282, 2012-2018 (1998)
Helicobacter pylori	J99	B	1.64	Astra Research Center Boston / Genome Therapeutics	Astra Research Center Boston / Genome Therapeutics	Alm *et.al., Nature*, **397**:176-180 (1999)

Leishmania major Chr1	Friedlin	E	0.27	SBRI		Myler *et al., Proc Natl Acad Sci USA* **96**: 2902-2906 (1999)
Chlamydia pneumoniae	CWL029	B	1.23	UC Berkeley & Stanford	Incyte	Kalman *et al., Nat Genet* **21**: 385-389 (1999)
Aeropyrum pernix	K1	A	1.67	Biotechnology Center	NITE	Kawarabayasi *et al., DNA Research* **6**: 83-101 (1999)
Thermotoga maritima	MSB8	B	1.80	TIGR	DOE	Nelson *et al., Nature* **399**: 323-329 (1999)
Plasmodium falciparum Chr 3	isolate 3D7	E	1.06	Sanger Centre	Wellcome Trust	Bowman *et. al., Nature* **400**:532-538 (1999)
Deinococcus radiodurans	R1	B	3.28	TIGR	DOE	White *et al., Science* **286**: 1571-1577 (1999)
Campylobacter jejuni	NCTC 11168	B	1.64	Sanger Centre	Beowulf Genomics	Parkhill *et al., Nature* **403**: 665-668 (2000)
Neisseria meningitidis	MC58	B	2.27	TIGR	Chiron Corp.	Tettelin *et al., Science* **287**: 1809-1815 (2000)
Neisseria meningitidis	serogroup A strain Z2491	B	2.18	Sanger Centre	Wellcome Trust	Parkhill *et al., Nature* **404**: 502-506 (2000)
Chlamydia trachomatis	MoPn	B	1.07	TIGR	NIAID	Read *et al., Nuc. Acids Res.* 28: 1397-1406 (2000)
Chlamydia pneumoniae	AR39	B	1.23	TIGR	NIAID	Read *et al., Nuc. Acids Res.* 28: 1397-1406 (2000)
Drosophila melanogaster				Celera Genomics		Adams et al., Science 287:2185-2195 (2000). Myers et al., Science 287:2196-2204 (2000). Rubin GM et al., Science 287-:2204-2215 (2000).

1B: Microbial genomes and chromosomes in progress (Searches available for some TIGR genomes)

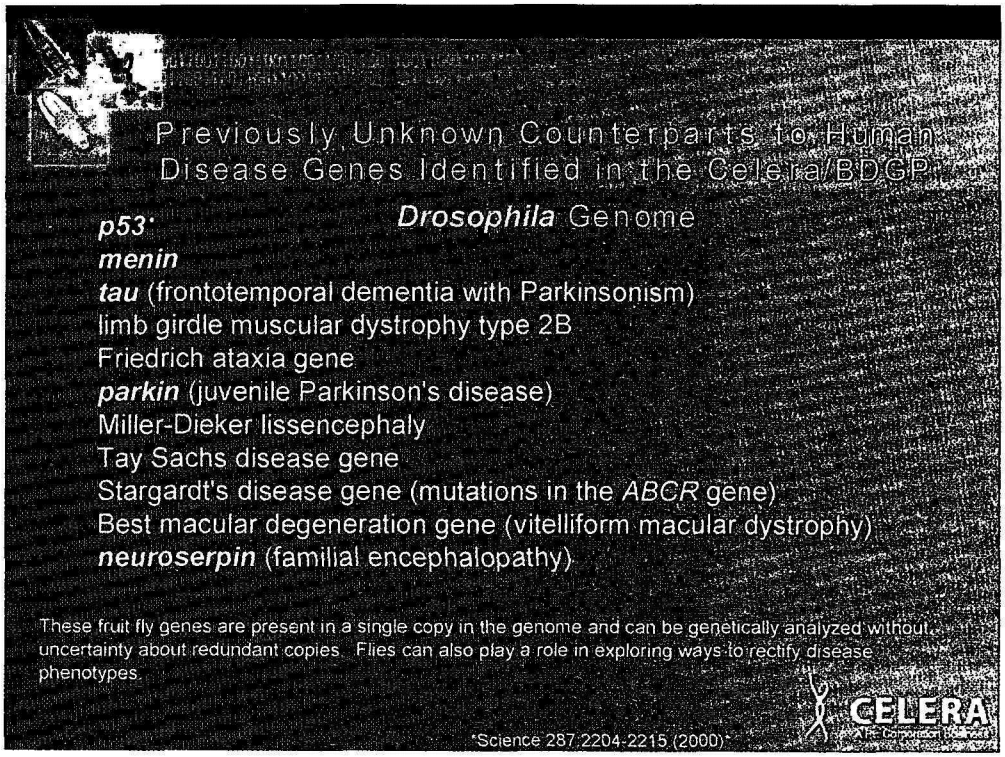
Genome	Strain	Domain	Size (Mb)	Institution	Funding	Anticipated Completion
Actinobacillus actinomycetemcomitans	HK1651	B	2.2	University of Oklahoma	NIDR	
Aspergillus nidulans		E	29	Cereon Genomics		
Bacillus anthracis BLAST Search	Ames	B	4.5	TIGR	ONR / DOE / NIAID	
Bacillus halodurans	C-125	B	4.2	Japan Marine Science and Technology Center		Complete
Bacillus stearothermophilus	10	B		Univ. of Oklahoma	NSF	
Bartonella henselae	Houston 1	B	2.00	University of Uppsala	SSF	2000
Bordetella bronchiseptica	RB50	B	4.9	Sanger Centre	Beowulf Genomics	
Bordetella parapertussis		B	3.9	Sanger Centre	Beowulf Genomics	
Bordetella pertussis	Tohama I	B	3.88	Sanger Centre	Beowulf Genomics	
Buchnera sp.	APS	B	0.64	Univ. Tokyo / RIKEN		Complete
Burkholderia pseudomallei	K96243	B	6.0	Sanger Centre / DERA / Public Health Laboratory	Beowulf Genomics	
Candida albicans	1161	E	15	Sanger Centre	Beowulf Genomics	
Candida albicans	SC5314	E		Stanford	NIDR / NIH / Burroughs Wellcome Fund	
Caulobacter crescentus BLAST Search		B	3.80	TIGR	DOE	
Chlamydia pneumoniae		B	1.23	Genset		Complete
Chlamydophila psittaci BLAST Search	GPIC	B	1.2	TIGR	NIAID	2000
Chlamydia trachomatis	L2	B	1.038	Genset		Complete
Chlorobium tepidum BLAST Search	TLS	B	2.10	TIGR	DOE	
Clostridium acetobutylicum	ATCC 824	B	4.1	Genome Therapeutics	DOE	
Clostridium difficile	630	B	4.4	Sanger Centre	Beowulf Genomics	
Corynebacterium diphtheriae	NCTC13129	B	3.1	Sanger Centre / W.H.O. / Public Health Laboratory	Beowulf Genomics	
Corynebacterium glutamicum	ATCC 13032	B	3.2	LION Bioscience	Degussa/IIT	2000
Dehalococcoides ethenogenes BLAST Search		B	1.5	TIGR	DOE	
Desulfovibrio vulgaris BLAST Search	Hildenboroug h	B	3.2	TIGR	DOE	
Dictyostelium discoideum Chr 2	AX4	E	7.0	University of Cologne/ University of Jena	DFG	
Dictyostelium discoideum Chr 6	AX4	E	4.0	Baylor College of Medicine/ Sanger Centre	NIH/ EU	
Encephalitozoon cuniculi		E	2.9	GENOSCOPE		Complete
Escherichia coli	O157:H7	B	5.6	Japanese Consortium		Complete
Enterococcus faecalis BLAST Search	V583	B	3.00	TIGR	NIAID	2000

Francisella tularensis	schu 4	B	2.00	European & North American consortium		
Geobacter sulfurreducens BLAST Search		B	2.50	TIGR / Univ of Massachusetts, Amherst	DOE	
Giardia lamblia	WB	E	12	Marine Biological Laboratory	NIAID	
Haemophilus ducreyi	35000	B	1.76	NIAID		
Halobacterium salinarium		A	4.0	Max-Planck-Institute for Biochemistry		
Halobacterium sp.	NRC-1	A	2.50	University of Massachusetts / University of Washington	NSF	2000
Klebsiella pneumoniae	M6H 78578	B		Washington University Consortium		
Lactobacillus acidophilus	ATCC 700396	B	1.9	Environmental Biotechnology Institute	Dairy Management, Inc. / California Research Foundation / Environmental Biotechnology Institute	
Lactococcus lactis	IL1403	B	2.35	GENOSCOPE		Complete
Legionella pneumophila	Philadelphia-1	B	4.0	Columbia Genome Center	NIAID	2002
Leishmania major Chr3	Friedlin	E		SBRI		
Leishmania major Chr4	Friedlin	E	0.5	Sanger Centre	Beowulf Genomics	
*Leishmania major*Chr5,13,14,19,21,23	Friedlin	E		Sanger Centre/European Consortium	European Commission	
Leishmania major Chr27	Friedlin	E		SBRI		
Leishmania major Chr35	Friedlin	E		SBRI		
Leptospira interrogans serovar icterohaemorrhagiae	Lai	B	4.8	Chinese National Human Genome Center at Shanghai	CNCBD/Science and Technology Commission of Shanghai	2000
Listeria innocua	Clip11262, rhamnose-negative	B	3.2	GMP	Institut Pasteur	2000
Listeria monocytogenes	EGD-e	B	2.94	EC Consortium	EC	Complete
Methanococcus maripaludis	JJ	A		University of Washington		
Methanogenium frigidum		A		UNSW / AGRF		
Methanosarcina mazei	G 1	A	2.8	Goettingen Genomics Laboratory	Ministry of Lower Saxony for Science and Culture	2000
Methylobacterium extorquens		B		University of Washington		
Methylococcus capsulatus		B	4.60	TIGR / University of Bergen, Norway	DOE	
Mycobacterium avium BLAST Search	104	B	4.70	TIGR	NIAID	2000

Mycobacterium bovis	AF2122/97	B	4.4	Sanger Centre / Institut Pasteur / VLA Weybridge	MAFF / Beowulf Genomics	
Mycobacterium leprae		B	2.80	Sanger Centre	The New York Community Trust	
Mycobacterium tuberculosis	CSU#93 (clinical isolate)	B	4.40	TIGR	NIAID	2000
Mycoplasma hyopneumoniae	232	B	0.89	University of Washington		Complete
Mycoplasma mycoides subsp. mycoides SC	PG1	B	1.28	The Royal Institute of Technology, Stockholm & The National Veterinary Institute, Uppsala	SSF	2000
Mycoplasma pulmonis		B	0.95	GENOSCOPE		
Neisseria gonorrhoeae		B	2.20	University of Oklahoma	NIAID	
Neisseria meningitidis	Serogroup C strain FAM18	B	2.2	Sanger Centre	Beowulf Genomics	
Neurospora crassa	74-OR23-IVA	E	43	Heinrich-Heine University Duesseldorf	DFG	
Nitrosomonas europaea		B	2.2	JGI	DOE	
Nostoc punctiforme	ATCC 29133	B	10	JGI	DOE	
Pasteurella haemolytica		B	2.4	LION Bioscience	BMBF/ HRVet	Complete
Pasteurella multocida BLAST Search	Pm70	B	2.4	University of Minnesota	USDA-NRI / Minnesota Turkey Growers Association	2000
Photorhabdus luminescens	TT01	B	5.5	GMP		2001
Plasmodium falciparum **Chr1,4,5,6,7,8,9,13** (isolate 3D7)		E		Sanger Centre	Wellcome Trust	
Plasmodium falciparum **Chr10,11** (isolate 3D7)		E	2.10	TIGR / NMRI	NIAID/ NIH/ DOD	
Plasmodium falciparum **Chr12** (isolate 3D7)		E	2.4	Stanford University	Burroughs Wellcome Fund	
Plasmodium falciparum **Chr14** (isolate 3D7)		E	3.4	TIGR/ NMRI	Burroughs Wellcome Fund/ DOD	
Pneumocystis carinii	f. sp. carinii	E	7.7	Univ. of Cincinnati/ National and International Consortium	NIAID	2004
Pneumocystis carinii	f. sp. hominis	E	7.5	Univ. of Cincinnati/ National and International Consortium	NIAID	2004
Porphyromonas gingivalis BLAST Search	W83	B	2.20	TIGR/ Forsyth Dental Center	NIDR	2000
Prochlorococcus marinus	MED4	B	2.00	JGI	DOE	
Pseudomonas aeruginosa	PAO1	B	5.90	University of Washington PathoGenesis	Cystic Fibrosis Foundation PathoGenesis	
Pseudomonas putida BLAST Search		B	6.1	TIGR/German Consortium	DOE/BMBF	
Pyrobaculum aerophilum		A	2.22	Caltech / UCLA	ONR / DOE	Complete
Pyrococcus abyssi	GE5	A	1.8	GENOSCOPE		Complete
Pyrococcus furiosus		A	2.10	Center of Marine Biotechnology / Univ. Utah	DOE	

Ralstonia solanacearum		B		GENOSCOPE		
Rhodobacter capsulatus	SB1003	B	3.70	University of Chicago / Institute of Molecular Genetics		2000
Rhodobacter sphaeroides	2.4.1	B	4.34	Univ. of Texas - Houston Health Science Center		
Rhodopseudomonas palustris		B	4.5	JGI	DOE	
Rickettsia conorii		B	1.2	GENOSCOPE		
Salmonella enteritidis	LK5	B	4.5	Univ. of Illinois	University of Illinois	
Salmonella paratyphi A	ATCC 9150	B	4.60	Washington University Consortium		
Salmonella typhi		B	4.5	Sanger Centre	Wellcome Trust	
Salmonella typhimurium	SGSC1412	B	4.80	Washington University Consortium		
Salmonella typhimurium	TR7095	B	4.50	Washington University Consortium		
Schizosaccharomyces pombe		E	14	Sanger Centre	Wellcome Trust	
Shewanella putrefaciens BLAST Search	MR-1	B	4.50	TIGR	DOE	
Shigella flexneri 2a	301	B	4.7	Microbial Genome Center	Chinese Ministry of Public Health	2000
Sinorhizobium meliloti	1021	B	6.6	European & Canadian Consortium / Stanford Univ.	European Union	2000
Staphylococcus aureus BLAST Search	COL	B	2.80	TIGR	NIAID / MGRI	
Staphylococcus aureus	8325	B	2.80	University of Oklahoma	NIAID / MGRI	
Staphylococcus aureus	MRSA	B	2.8	Sanger Centre / Trinity College / WTCEID	Beowulf Genomics	
Staphylococcus aureus	MSSA	B	2.8	Sanger Centre / Trinity College / WTCEID	Beowulf Genomics	
Streptococcus agalactiae	ATCC 12403	B	2.00	GMP	M.E.N.R.T.	2001
Streptococcus mutans	UAB159	B	2.20	University of Oklahoma	NIDR	
Streptococcus pneumoniae BLAST Search	type 4	B	2.20	TIGR	TIGR / NIAID / MGRI	2000
Streptococcus pneumoniae	R6	B	2.04	Eli Lilly		Complete
Streptococcus pyogenes	M1	B	1.85	University of Oklahoma	NIAID	
Streptococcus pyogenes	Manfredo	B	1.98	Sanger Centre / Univ. of Newcastle	Beowulf Genomics	
Streptomyces coelicolor	A3(2)	B	8.0	Sanger Centre / John Innes Centre	BBSRC/ Beowulf Genomics	2000
Sulfolobus solfataricus		A	3.05	Canadian & European Consortium		
Synechococcus spp.		B		JGI	DOE	
Thermoplasma acidophilum		A	1.7	Max-Planck-Institute for Biochemistry		
Thermoplasma volcanium	GSS1	A		AIST		
Thermus thermophilus	HB27	B	1.82	Goettingen Genomics Laboratory	Ministry of Lower Saxony for Science and Culture	2000
Thiobacillus ferrooxidans	ATCC 23270	B	2.90	TIGR	DOE	
Treponema denticola		B	3.00	TIGR/ Univ. Texas		
Trypanosoma brucei Chr1	TREU 927/4	E	1.1	Sanger Centre	Beowulf Genomics	
Trypanosoma brucei BLAST Search	GuTat10.1	E	35	TIGR	NIAID	

Ureaplasma urealyticum	serovar 3	B	0.75	**U. Alabama / PE-ABI**	**PE-ABI / NIH / UAB**	2000
Ustilago maydis		E	20	**LION Bioscience**	**Bayer**	2000
Vibrio cholerae BLAST Search	serotype O1, Biotype El Tor, strain N16961	B	4.0	**TIGR**	**NIAID**	2000
Xanthomonas citri		B	5.3	**Brazilian Consortium**	**FAPESP**	2001
Xylella fastidiosa	8.1.b clone 9.a.5.c	B	2.7	**Brazilian Consortium**	**FAPESP**	Complete
Yersinia pestis	CO-92 Biovar Orientalis	B	4.38	**Sanger Centre**	**Beowulf Genomics**	


Previously Unknown Counterparts to Human Disease Genes Identified in the Celera/BDGP *Drosophila* Genome
p53
menin
tau (frontotemporal dementia with Parkinsonism)
limb girdle muscular dystrophy type 2B
Friedrich ataxia gene
parkin (juvenile Parkinson's disease)
Miller-Dieker lissencephaly
Tay Sachs disease gene
Stargardt's disease gene (mutations in the *ABCR* gene)
Best macular degeneration gene (vitelliform macular dystrophy)
neuroserpin (familial encephalopathy)
These fruit fly genes are present in a single copy in the genome and can be genetically analyzed without uncertainty about redundant copies. Flies can also play a role in exploring ways to rectify disease phenotypes.
CELERA
Science 287:2204-2215 (2000)

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