جائزة الملك فيصل العالمية
King Faisal International Prize

# ARTICLES IN MEDICINE AND SCIENCE VI

THE 2006
KING FAISAL
INTERNATIONAL PRIZE

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**Custodian of the Two Holy Mosques**
**King Abd Allah Ibn Abdul Aziz Al-Saud**
Patron of the King Faisal Foundation

# Contents

# INTRODUCTION

The King Faisal Foundation continues the traditions of Arabic and Islamic philanthropy, as they were revitalized in modem times by King Faisal. The life and work of the late King Faisal bin 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 (US$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.

Nominations for the Prizes are accepted from academic institutions, research centers, professional organizations and other learned circles worldwide. After preselection by expert reviewers, the. Short-listed 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 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.

(Excerpt from Introduction to 'Articles in Medicine and Science 1"
by H.R.H. Khaled Al Faisal,
Chairman of the Prize Board and
Director General of King Faisal Foundation)

## 2006 Prize Awards in Medicine and Science

The 2006 awards were presented in April 2006

The Prize for Medicine (Topic: Biology of Vascular Inflammation) has been awarded to: Professor Michael Anthony Gimbrone, Jr. (USA)

Professor of Pathology, Harvard Medical School, and Chairman of the Department of Pathology at Brigham and Women's Hospital. Professor Gimbrone, Jr., has more than 250 publications in renowned international journals over the past 4 decades. He has made fundamental contributions to the field of vascular biology. He has pioneered the culturing of human endothelial and smooth muscle cells, and discovered endothelial leucocyte adhesion molecules. He identified three genes with potential arthroprotective activities. He developed a novel in vitro flow model to simulate pulsatile shear stress waveforms encountered by the endothelium in the arterial circulation which reveals the unique responsiveness of endothehal cells.

The prize for Science (Topic: Mathematics) has been awarded jointly to: Professor Simon Kirwan Donaldson (UK), President of the Institute of Mathematical Sciences, and Professor of Mathematics at Imperial College, London and Professor Mudumbai Seshachalu Narasimhan (India) Honorary Fellow, Tata Institute of Fundamental Research in India for their seminal contributions to theories which have strengthened the links between mathematics and physics, and helped provide a rigorous foundation for physical theories giving a very good description of the laws of matter at the sub-nuclear level. This has helped establish strong ties with the formulation of quantum chromodynamics for which the King Faisal Prize was given last year (in physics).

WINNER OF THE 2006
KING FAISAL INTERNATIONAL PRIZE
FOR MEDICINE


Medal: King Faisal International Prize for Medicine

**Professor Michael Anthony Gimbrone, Jr.**

**Winner of the 2006 King Faisal International Prize for Medicine**

Synopsis of Achievements
Professor Michael Anthony Gimbrone, Jr.

Professor Michael A. Gimbrone Jr. is one of the world's most accomplished and creative vascular biologists. Born in Buffalo, New York (U.S.A.) in 1943, he received his B.A. degree in Zoology (*Summa cum laude*) from Cornell University and his M.D. degree (*Magna cum laude*) from Harvard Medical School. After completing an Internship in Surgery at the Massachusetts General Hospital and a Research Fellowship at the Children's Hospital Medical Center in Boston, he became a Staff Associate at the National Cancer Institute in Bethesda, Maryland. He then pursued Residency Training in Pathology at the Peter Bent Brigham Hospital in Boston in 1974, and was appointed an Instructor in Pathology at Harvard Medical School in 1975 and subsequently rose through the academic ranks to Professor of Pathology in 1985. He established and currently directs the Center for Excellence in Vascular Biology at the Brigham and Women's Hospital in Boston, and is the Elsie T. Friedman Professor of Pathology at Harvard Medical School and Chairman of the Department of Pathology at the Brigham and Women's Hospital.

Professor Gimbrone's outstanding contributions to the field of vascular biology, particularly the biology of vascular inflammation, have established the conceptual framework for understanding the mechanistic role of the endothelial lining of the cardiovascular system in diseases such as atherosclerosis and its complications-- heart attack and stroke. He pioneered the growth of human vascular endothelial and smooth muscle cells *in vitro*; was the first to show that endothelial cells produce prostaglandins and other mediators that influence the function of blood platelets and leukocytes; established the paradigm of endothelial activation by pro-inflammatory cytokines and discovered inducible endothelial-leukocyte adhesion molecules that are important in inflammation and atherogenesis. His laboratory also identified the first biomechanically activated "shear stress-response element" in the promoter of a human gene, and has gone on to apply high-throughput genomic analyses to identify "athero-protective genes" that appear to confer resistance to pro-inflammatory stimuli and the development of atherosclerotic lesions in the cardiovascular system. These studies point the way to new methods for the diagnosis, treatment and prevention of vascular disease.

These seminal contributions have appeared in more than 250 publications, reviews and book chapters, and have earned Professor Gimbrone worldwide recognition. Among the numerous awards received by Gimbrone are: the Established Investigatorship Award from the American Heart Association, the J. Allyn Taylor International Prize in Medicine, the Warner Lambert/Parke Davis Award in Experimental Pathology, the Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research, the Pasarow Foundation Award in Cardiovascular Disease, the Basic Research Prize from the American Heart Association, and a MERIT Award from the U.S. National Heart, Lung and Blood Institute. His honors also include an impressive list of distinguished visiting professorships and lectureships in the U.S.A., Europe and Japan, memberships of editorial boards of leading medical journals, and election to prestigious institutions such as the National Academy of Sciences (U.S.A.), the American Academy of Arts and Sciences, and the Institute of Medicine of the National Academy of Sciences. He is a past President of the American Society for Investigative Pathology and the founding President of the North American Vascular Biology Organization.

# Biology of Vascular Endothelium in Health and Disease: New Insights

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Chairman, Department of Pathology
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## Vascular Biology: An Emerging Discipline.

Essential to any integrated functional view of the cardiovascular system is an appreciation of the vasculature as more than simply a branched array of varying sized tubes that convey blood. In recent years, blood vessels, *per se*, have become the focus of multidisciplinary studies that have greatly expanded our understanding of their intrinsic functions, and, in the process, many of our working concepts of cardiovascular biology and medicine have been redefined—and a new discipline, *Vascular Biology,* has emerged. The *anatomist*, probing the ultrastructure of arteries, capillaries and veins, has uncovered specializations in luminal endothelial membranes, microvesicles, cell-cell junctions and cytoskeletal architecture, suggestive of regionally specialized functions. The *physiologist*, measuring systemic indices such as blood pressure, as well as local phenomena such as regional permeability, has revealed elaborate regulatory networks that impact on cardiac performance and peripheral tissue nutrition. The *pathologist*, investigating the mechanisms of complex vascular diseases such as atherosclerosis, has uncovered elements shared in common with basic "response-to-injury" processes such as inflammation, wound healing and angiogenesis. And, the *vascular cell biologist*, by selectively dissociating the blood vessel into its component cell types --- intimal endothelial cell, medial smooth muscle cell (or pericyte) and adventitial fibroblast, has enabled the detailed investigation of each, in biochemical, cell biological and molecular biological terms. This latter approach has contributed to the formulation of a highly dynamic working concept of a blood vessel as a "community of cells" engaged in multiple, reciprocal interactions among themselves, and with circulating macromolecules (e.g., lipoproteins, hormones) and blood elements (e.g., leukocytes, erythrocytes, platelets). In health, an orderly balance of these interactions maintains homeostasis within the cardiovascular system, whereas, imbalances in the same interactions, in response to pathophysiologic stimuli, can contribute to the initiation and progression of vascular disease.

**Vascular Endothelium: A Multifunctional Interface.**

The vascular endothelium, the single-cell-thick, continuous lining of the circulatory system, forms a multifunctional interface between circulating blood and the various tissues and organs of the body. It constitutes a selectively permeable barrier for macromolecules, as well as non-thrombogenic container that actively maintains the fluidity of blood. It is a metabolically active tissue, serving as the source of multiple factors (peptides, proteins, lipids) that are critical for normal homeostasis. These include growth stimulators and inhibitors (e.g., platelet-derived growth factor, transforming growth factor-beta), fibroblast growth factor, and heparin-like glycosaminoglycans); vasoconstrictors and vasodilators (e.g., endothelin-1, angiotensin II, and endothelial-derived relaxing factors, such as nitric oxide); the various pro- and anti-thrombotic factors (e.g., tissue factor, thrombomodulin, and von Willebrand factor); fibrinolytic activators and inhibitors (e.g., tissue plasminogen activator, urokinase, and plasminogen activator inhibitor-1); potent arachidonate metabolites (e.g., prostacyclin); leukocyte adhesion molecules (e.g., E-Selectin, P-Selectin, ICAM-1, and VCAM-1) and multiple cytokines (e.g., IL-1, IL-6, IL-8, MCP-1, and GM-CSF). This partial list underscores the functional diversity of the endothelial interface in normal physiology and also illustrates its potential contributions to pathophysiological processes in vascular disease.

**Endothelial Dysfunction and the Pathogenesis of Atherosclerosis.**

The involvement of vascular endothelium in complex vascular disease processes such as atherosclerosis has been recognized since the time of Virchow (*circa* 1855), but a working knowledge of the relevant pathobiology has been developed only recently, largely as a result of the application of modern cellular and molecular biological techniques. It has been our laboratory's working concept that the vascular endothelium is a dynamically mutable interface, whose structural and functional properties are responsive to a variety of stimuli, both local and systemic, and further, that its phenotypic modulation to a dysfunctional state can constitute a pathogenic risk factor for vascular diseases. In the arterial wall, certain consequences of endothelial dysfunction are directly related to the pathogenesis of atherosclerosis and its complications. These include: altered vascular reactivity and vasospasm; altered intimal permeability to lipoproteins; enhanced mononuclear leukocyte recruitment and intimal accumulation as foam cells; altered vascular cell growth regulation (e.g., decreased endothelial regeneration, increased smooth muscle proliferation); and altered hemostatic/fibrinolytic balances (favoring thrombin generation, platelet and fibrin deposition). Pathophysiologic stimuli of arterial endothelial dysfunction that are especially relevant to atherogenesis include: activation by cytokines and bacterial endotoxins; infection (and possible transformation) by viruses; advanced glycosylation endproducts (AGEs) that are generated in diabetes and with aging; hyperhomocysteinemia; and hypercholesterolemia (*per se*), as well as oxidized lipoproteins and their components (e.g., lyso-phosphatidylcholine). In addition to these humoral stimuli, it is now clear that biomechanical forces, generated by flowing blood, can also influence the structure and function of endothelial cells, and even modulate their expression of pathophysiologically relevant genes.

The possibility that hemodynamic forces can act as pathophysiologic stimuli for endothelial dysfunction provides a conceptual rationale for the long-standing observation that the earliest lesions of atherosclerosis characteristically develop in a non-random pattern, the geometry of which correlates with branch points and other regions of altered blood flow.

**Biomechanical Forces Generated by Blood Flow Can Regulate Genes Important in Inflammation and Atherosclerosis in Vascular Endothelial Cells.**

In the early 1980's, our laboratory began a long-term collaboration with bioengineering colleagues at the Massachusetts Institute of Technology with the goal of recreating, in the environment of a cultured endothelial cell, the fluid mechanical stimuli that are present within the cardiovascular system *in vivo.* Early work focused on the design of special apparatuses that could generate well characterized fluid shear stresses (laminar, disturbed laminar, turbulent flows) on the surfaces of cultured human and animal endothelial monolayers, over a broad dynamic range that could mimic arterial and venous, as well as microvascular, circulatory dynamics. Utilizing this approach, our research group obtained the first direct evidence that endothelial cell structure and function were dynamically responsive to applied mechanical forces (in particular, cell shape, actin cytoskeletal organization and cell cycle regulation), and characterized certain of the stimulus-response/second messenger pathways involved.

In the early 1990's, our group extended these studies to the level of the nucleus by the discovery and characterization of a unique cis-acting transcriptional regulatory element in the promoter of the PDGF-B gene that was necessary and sufficient for the induction of gene expression by biomechanical forces. This "shear stress response element" (SSRE) also was found in the promoters of several other pathophysiologically relevant endothelial genes (e.g., endothelial nitric oxide synthase, cyclooxygenase-2, tissue plasminogen activator, ICAM-1) whose expression is sensitive to physiological levels of shear stress, thus suggesting that it may be part of a common pathway of gene regulation by mechanical stimulation. This was further supported by the demonstration of the activation of the SSRE by other biophysical forces including cyclic strain. Since the original description of the SSRE in the human PDGF-B gene, several additional pathways of gene regulation in endothelium by biomechanical stimuli have been uncovered by our research group and others.

Prompted by the observation that the earliest lesions of atherosclerosis (a chronic inflammatory disease of arteries) characteristically develop in a non-random pattern in the vasculature, (with lesion-prone areas localized to arterial branch points and lesion-protected areas localized to straight tubular geometries), we hypothesized that this pattern of disease development reflects an underlying pattern of differential regulation of endothelial gene expression by fluid mechanical forces. Utilizing high-through-put differential gene display, our laboratory has systematically compared the patterns of endothelial genes regulated by defined biomechanical stimuli (steady laminar flow versus disturbed laminar and turbulent flows). This novel strategy led to the identification of at least three endothelial genes (endothelial nitric oxide synthase, cyclooxygenase-2, Mn-superoxide dismutase) which are selectively upregulated by steady laminar but not turbulent shear stresses, and whose anti-vasospastic, anti-inflammatory, anti-oxidant activities would be predicted to be "athero-protective". Interestingly, the prediction that COX-2 would function as an "athero-protective gene" in human endothelium has been borne out by the recent adverse human clinical trials data with selective COX-2 inhibitors (such as Vioxx) showing a markedly increased cardiovascular risk. In addition, several new human genes, which show differential regulation by biomechanical forces in vascular endothelial cells, have been cloned and their functional roles are currently being evaluated in both *in vitro* and *in vivo* models.

**Genome-Wide Analysis of Proinflammatory Phenotype of Vascular Endothelium and Natural Anti-Inflammatory Control Mechanisms.**

Most recently, our group has harnessed the power of high-density cDNA microarrays, and newly devised bioinformatics tools, to accomplish the most comprehensive analysis to date of the genome-wide "transcriptome" of the human endothelial cell, as modulated by various biomechanical and biochemical stimuli, relevant to vascular biology and vascular inflammation. A dramatic demonstration of the power of this experimental strategy has been the recreation of the precise hemodynamic waveforms that occur in distinct anatomical parts of the human carotid artery, which are characteristically either *resistant* or *susceptible* to the development of atherosclerotic lesions, on the surface of cultured human endothelial cells, and the analysis of the resultant patterns of gene expression. Bioinformatic analyses of the comprehensive expression profiles obtained (encompassing approximately 35,000 distinct genes) revealed that only approximately 100 genes show significant *differential regulation* (i.e., up- or down-regulation by the "atheroprotective" versus "atheroprone" waveforms). Several of these genes are known to be important in the pathophysiology of atherosclerosis, including leukocyte adhesion molecules, chemokines and their receptors, growth regulators and anti-oxidative stress factors. Interestingly, further analysis has identified biomechanically sensitive transcriptional regulators that appear to function as "master-switches" for the pro- vs. anti-inflammatory phenotype in the vascular endothelial cell. Indeed, one of these transcriptional "switches", Kruppel-like Factor-2 (KLF2), appears to be a primary regulator of the biomechanically induced "atheroprotective" phenotype in the human endothelial cell. Recent studies by our group and others have now established that KLF2 is sensitive to the Statin class of therapeutic drugs—thus establishing a *direct* mechanistic link between these compounds (currently taken by millions of people worldwide) and athero-protective effects on the endothelial cell. Further analysis of the transcriptional programs induced by "atheroprotective" waveforms should provide new insights into the mechanisms by which endothelial cells act to maintain vascular integrity in health, and potentially will facilitate the development of new classes of vascular protective drugs for the treatment and prevention of cardiovascular disease. (Figures 1 & 2).

This novel line of investigation has thus established a new paradigm of endothelial activation--differential gene regulation by biomechanical forces, which promises to provide new basic insights into the molecular mechanisms of host defense and vascular inflammation. These studies hopefully will find practical translation to better means for the early detection, effective treatment, and ultimately prevention of cardiovascular diseases, including heart attacks and strokes.

**Acknowledgments:**

Original studies summarized in this review were supported primarily by grants from the National Heart, Lung and Blood Institute of the National Institutes of Health (U.S.A.). The author wishes to acknowledge the collaboration of Prof. C.F. Dewey and R. Kamm and colleagues at the Massachusetts Institute of Technology; all of the members (past and present) of the Vascular Research Division of the Department of Pathology at the Brigham and Women's Hospital; Drs. R. W. Alexander, M. Bevilacqua, B. Blackman, T. Collins, M. Cybulsky, G. Dai, P. F. Davies, G. Garcia-Cardena,P. Libby, F. W. Luscinskas, J. Pober, N. Resnick, J. Topper; and his late mentor, Ramzi Suliman Cotran.

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Figure 1

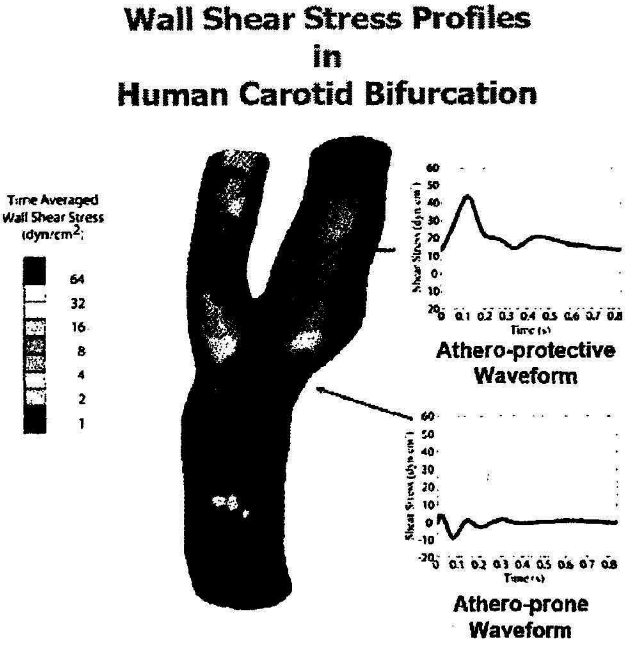


**Figure 1: Hemodynamic Analysis of Regions of the Human Carotid Artery that are Characteristically Resistant or Susceptible to the Development of Atherosclerotic Lesions.**
The wall shear stresses generated by the pulsatile flow of blood in the vicinity of the bifurcation of human carotid artery were analyzed by computational fluid mechanics, and prototypic waveforms characteristic of those present *in vivo* in atherosclerosis-resistant and atherosclerosis-susceptible areas were identified. These biomechanical stimuli were then recreated, utilizing a Dynamic Flow Device, on the surface of cultured human endothelial monolayers *in vitro*, and the patterns of endothelial gene regulation were defined, utilizing high-throughput genomic analysis and bioinformatics techniques (see Reference 12).

Figure 2

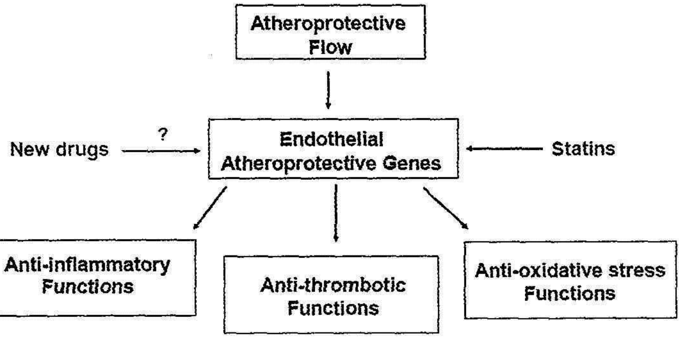


**Figure 2: Biomechanical Stimulation of Atheroprotective Phenotype in Vascular Endothelium and its Mimicry by Therapeutic Agents.**

Biomechanical forces generated by blood flow in certain vascular geometries that are *resistant* to the development of atherosclerotic lesions (see Figure 1) act to regulate the expression of "atheroprotective genes". These genetic programs result in functional changes that render the vascular endothelial lining in these regions resistant to inflammatory, thrombotic and oxidative stresses. The Statin class of cardiovascular drugs, which are known to prevent atherosclerosis via actions in addition to lipid-lowering, can act directly on endothelium to mimic this natural "atheroprotective" biomechanical stimulation. This novel paradigm of biomechanical stimulation of atheroprotective genes may enable the discovery of new drugs that will be effective in preventing atherosclerosis and its complications (see References 13-15).

# WINNERS OF THE 2006
# KING FAISAL INTERNATIONAL PRIZE
# FOR SCIENCE


Medal: King Faisal International Prize for Science

**Professor Simon Kirwan Donaldson**
**Co-Winner of the 2006 King Faisal International Prize for Science**

Synopsis of Achievements

# Professors Simon Kirwan Donaldson And M. S. Narasimhan

SIMON DONALDSON and M. S. NARASIMHAN have been jointly awarded the 2006 King Faisal International Prize for Science. The prize, presented by the King Faisal Foundation, consists of a gold medal and a cash prize of US$200,000, which the two recipients will share.

Born in 1957 in Cambridge, England, Simon Kirwan Donaldson received his Ph.D. in 1983 from Oxford University, under the direction of Michael Atiyah. Donaldson was a professor at Oxford University and at Stanford University before becoming a professor at Imperial College, London. He is now a Royal Society Research Professor at Imperial and also serves as president of Imperial's Institute of Mathematical Sciences. His many honors include the Fields Medal (1986) and the Crafoord Prize (1994). He is a fellow of the Royal Society, London. Donaldson's early research revolutionized four-dimensional differential topology, revealing surprising new phenomena through the application of ideas from gauge theory. He has also made foundational contributions to complex and symplectic geometry and to global analysis of partial differential equations on manifolds.

Mudumbai Seshachalu Narasimhan was born in 1932 in Thandarai, in the state of Tamiladu, in India. He received his Ph.D. from the University of Bombay in 1960, under the direction of Komaravolu Chandrasekharan. For many years Narasimhan was a professor at the Tata Institute of Fundamental Research in Mumbai. In 1992, he went to the International Centre for Theoretical Physics in Trieste, where he headed the research group in mathematics. He is now an Honorary Fellow of the Tata Institute of Fundamental Research in India. In 1975 he received the Bhatnagar Prize for Mathematics (1975), which is the most prestigious award given in India. He also received the Third World Academy Award for Mathematics in 1987 and is a Fellow of the Royal Society, London. Narasimhan is a pioneer of the study of moduli spaces of holomorphic vector bundles on projective varieties. His work on projectively flat connections was the starting point for the development of the so-called Kobayashi-Hitchin correspondence linking the differential and algebraic geometry of vector bundles over complex manifolds.

The close connection between the research of the two prize inners is illustrated by the fact that one of Donaldson's earliest papers bears the title "A New Proof of a Theorem of Narasimhan and Seshadri" (*Journal of Differential Geometry*, 1983),referring to the landmark paper "Stable and Unitary Vector Bundles on Compact Riemann Surfaces", by Narasimhan and C. S. Seshadri (*Annals of Mathematics*, 1965). Narasimhan's paper with S. Ramanan on universal connections ("Existence of universal connections", *American Journal of Mathematics*, 1961 and 1963) has been very influential in the exchange of ideas between mathematics and theoretical physics surrounding index theory and gauge theory. This exchange of ideas is also the context for much of Donaldson's important work.

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## Differential Geometric Methods in Low-dimensional Topology

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### 1 Introduction

This is a survey of various applications of analytical and geometric techniques to problems in manifold topology. The author has been involved in only some of these developments, but it seems more illuminating not to confine the discussion to these.

We begin by recalling the notion of a manifold. Suppose we are provided with a large collection of small paper discs. Then we can construct a wide variety of complicated objects by pasting these discs together in various fashions. Mathematically, the paper discs generalise to disjoint copies $U\alpha$ of the unit ball Bn in some fixed Euclidean space Rn, where $\alpha$ ranges over some index set. The pasting data generalises to a collection of homeomorphisms$\varphi\alpha\beta$ : $U0\alpha\beta \rightarrow U00\ \alpha\beta$, where $U0\alpha\beta$ _ $U\alpha$ and $U00\ \alpha\beta$ _ $U\beta$ are open subsets. Then we form a space M byidentifying, in an abstract way, each point x in each $U0\alpha$ with its image $\varphi\alpha(x)$ in $U00\ \alpha$, and such a space is called an n-dimensional manifold. The essential point is that a manifold is locally modelled on Euclidean space, so we can ransfer many familiar constructions from multi-dimensional geometry and calculus to this wider setting. It is important to emphasise that this notion of a manifold does not just derive from mathematicians fancy, but grows naturally out of many diverse applications, often in Mathematical Physics. Most obviously, one formulates General Relativity in terms of a four-dimensional space-timemanifold.

The basic problem of geometric topology is to classify manifolds. More precisely, for our discussion, we want to consider manifolds constructed using differentiable maps (which allow us to do calculus): these lead to the definition of a "smooth" manifold, and the natural equivalence relation is that of "diffeomorphism". So, for each dimension n we are interested in classifying smooth n-dimensional manifolds up to diffeomorphism. For example, in two dimensions, any ellipsoid in R3 is diffeomorphic to the sphere, but a hyperboloid is not.

This classification problem has two complementary parts. In one direction, one seeks invariants of manifolds: the oldest example being the Euler characteristic which is an integer $\chi(M)$ one can assign to any (compact) manifold M, such that $\chi(M) = \chi(M0)$ if M and M0 are diffeomorphic. In the complementary direction, one seeks to construct diffeomorphisms $f : M \rightarrow M0$ showing that a pair of manifolds M,M0 are equivalent, under suitable hypotheses.

Over the 100 years since Poincar′e introduced the notion of a manifold, and hence this classification problem, many different strands have been developed. In this article we focus on constructions using differential geometry and analysis. The interesting feature here is that these methods call in techniques and ideas from other subjects, which do not ostensibly enter into the classification problem as we have formulated it. This means that we consider manifolds with some additional auxiliary structure such as a Riemannian metric, though this structure may disappear from the statement of the final result. A striking this, which probably has deep origins, is that these techniques are usually most relevant in "low-dimensional" topology, specifically when we consider n-dimensional manifolds with $n \leq 4$. In "high dimensions" ($n \geq 5$) a very rich theory was developed, particularly in the period 1950-1970. In brief, the subject of algebraic topology gives a systematic understanding of possible invariants and a fundamental result of Smale, the "h-cobordism theorem" yields a very powerful and general abstract technique for constructing diffeomorphisms between manifolds with the same invariants.

## 2 Two dimensions

The classification of two-dimensional manifolds is comparatively straightforward and has been known in some form since the mid 19th. century. nevertheless it is interesting to see how geometric and analytical techniques can be brought to bear on this, as a model for developments in higher dimensions.
Consider first the issue of invariants. Suppose we have a closed surface S _ R3 we can consider the flow of an imaginary fluid on the surface, or in mathematical terms a vector field v (the velocity field of the fluid) defined on S and everywhere tangent to S. In this way, we are lead to study a pair of partial differential equations

$$\operatorname{div}(v) = 0\ , \operatorname{curl}(v) = 0$$

for a tangent vector field v, corresponding to incompressible, irrotational flows. These are linear equations so the solutions form a vector space of dimension d(S) (which could a priori be infinite). It turns out that d(S) is finite and is unchanged if we continuously deform the surface in 3-space. Moreover we can extend the ideas further to an abstract two-dimensional manifold M equipped with a Riemannian metric. This metric is just the data required to define lengths and angles between tangent vectors at the same point and in turn the notions of divergence and curl. There is an enormous space of possible Riemannian metrics. In local co-ordinates (i.e. a local identification of the surface with a ball in **R**2)– say u1, u2–a metric is given by any functions gij(u1, u2) for i, j = 1, 2, subject only to the constraint that for each fixed u1, u2 the matrix with entries gij issymmetric and positive definite. The upshot is that , changing notation, we now have an integer d(M, g) where g denotes any choice of Riemannian metric out of this enormous space of possibilities. Now the crucial thing is that one can show that d(M, g) does not change if we deform the metric in a continuous fashion.So we conclude that this dimension is actually an invariant of the manifold M.

All the ideas above are now very well understood. The dimension d is just2–$\chi$(M) where $\chi$ is the Euler characteristic, which can be defined in many other ways. The ideas extend to higher dimensions in the form of "de Rham cohomology" and "Hodge theory", and the more general setting involves the machinery of "differential forms" rather than vector fields. At a more sophisticated level, one encounters the Dirac equation for fields of spinors on a manifold, and the Atiyah-Singer index theorem. One gets many invariants of manifolds, of any dimension, in this way, by studying the solutions of linear partial differential equations, but broadly speaking these can all be obtained in other ways, using the tools of algebraic topology.

Next we turn to the complementary question of constructing diffeomorphisms between 2-dimensional manifolds. Suppose for example that we want to show that any manifold M with $\chi$(M) = 2 is diffeomorphic to the standard sphere. One geometric approach to this goes via proving the existence of a particular Riemannian metric on the manifold. In classical differential geometry one defines, at each point of a surface in R3 the Gauss curvature of the surface: a natural generalisation of the notion of the curvature of a curve in the plane. The content of Gauss' famous "Theorem Egregium" is essentially that the Gauss curvature can be defined for any Riemannian metric on a general 2-dimensional manifold M. So we can search for metrics with constant Gauss curvature and in particular in the case at hand, with Gauss curvature 1. Then it is quite an easy exercise in differential geometry to show that if we have such a metric g on our manifold there is a unique diffeomorphism $f : M \rightarrow S2$ (up to rotations of the sphere) which takes g to the standard metric: in particular M is indeed diffeomorphic to the sphere.

So much for the overall strategy of this approach: we are left with the crucial problem of how to prove the existence of a Riemannian metric of Gauss curvature 1 on an abstract manifold M2, using only the hypothesis that $\chi(M) = 2$. This can be viewed as solving a complicated nonlinear partial differential equation for the unknowns gij . The easiest way to proceed is to bring in another kind of structure, that of a Riemann surface, but we will not go into details. Suffice it to say that the hypothesis $\chi(M) = 2$ enters through the assertion that there are no non zero abstract "fluid flows"of the kind considered above, and the Fredholm alternative from Functional Analysis.

**3 Three dimensions**

Exciting recent developments make it natural to include some brief discussion of 3-dimensional manifolds in our account, although this is not an area the author has contributed to personally.

First, the question of invariants. Over the past twenty years new 3-manifold invariants of various kinds have been discovered, having fundamental connections with geometry. On the one hand there are invariants such as the Casson invariant and Floer homology groups which are the 3-dimensional counterparts of the ideas in 4-dimensions discussed below. On the other hand there are the "Jones-Witten invariants" which, in Witten's point of view, arise from certain Quantum Field Theories.

Second, the question of constructing diffeomorphisms between 3-manifolds. The famous problem here is the "Poincar´e conjecture" which is that any simply connected compact 3-manifold is diffeomorphic to the 3-dimensional sphere. This is the natural analogue of the question about 2-dimensional manifolds discussed above, with the "simply connected" hypothesis in place of the condition on the Euler characteristic. There has been striking progress on this problem recently, through work of G. Perelman [5], which makes it seem very likely that this famous problem has now been resolved, and the strategy of proof follows that in our two-dimensional model. A Riemannian metric in higher dimensions has, in place of the simple Gauss curvature, a complicated curvature tensor.

From this one forms a slightly simpler object: the Ricci tensor $R_{ij}$ . This is what enters into Einstein's formulation of General Relativity, and one can write down an analogue of Einstein's equation in the context of Riemannian geometry: $R_{ij} = \lambda g_{ij}$ , where $\lambda$ is a constant. In three dimensions it turns out that the Ricci tensor contains the same information as the full curvature tensor, and using this it is easy to show that a simply-connected 3-manifold which admits a solution of the Einstein equation is diffeomorphic to the 3-sphere. So the problem is how to construct such Riemannian metrics.

Perelman's work follows a strategy developed over many years by R. Hamilton. One introduces an extra "time" variable t and considers a 1-parameter family of Riemannian metrics on a 3-manifold satisfying the evolution equation

$$\frac{\partial g_{ij}}{\partial t} = -R_{ij} .$$

Starting with an arbitrary initial metric at $t = 0$ one seeks to show that, after suitable rescaling, the metrics generated by this evolution equation converge to a solution of Einstein's equation. There are immense difficulties in carrying this through, but it appears that the crucial problems have been overcome by Perelman. This approach is not limited to the Poincar´e conjecture. In the 1970's W.Thurston formulated a "Geometrisation conjecture" which asserts that any 3-manifold can be decomposed in a standard and well-controlled way into pieces each of which admits an Einstein metric or one of a small family of other special structures. This is a much more wide-ranging conjecture which in a sense gives a complete classification of 3-manifolds and it is this which is the natural target for Perelman and Hamilton's work.

## 4 Four dimensions

### 4.1 Invariants

We now turn to four dimensional manifolds, the topic to which the author has contributed. Standard algebraic topology provides certain tools. We restrict attention to compact, simply-connected 4-manifolds with a fixed orientation. Then the algebro-topological data associated to such a manifold M is the free Abelian group $H_2(M)$ and the intersection form Q, which is a symmetric bilinear form on $H_2(M)$. The natural "grand problem"in the field is to classify, for each algebraic isomorphism class of the data $(H_2,Q)$ the possible diffeomorphism classes of manifolds. Roughly speaking, almost nothing was known about this question until the early 1980's but now we know a substantial amount through the emergence of the instanton and Seiberg-Witten invariants. However the problem itself still seems way out of reach, as we will discuss further below.

The general strategy by which these invariants are defined follows the same pattern as in the two-dimensional model discussed above. The crucial ingredientis the existence of certain geometrical objects and partial differential equations governing them, which play the role of the vector field and the irrotational, divergence-free conditions there. As in that model, the objects arise naturally from considerations in Mathematical Physics, although now that of fields andelementary particles rather than fluids.

A great achievement of 19th. century Mathematical Physics was the formulation of electro-magnetic theory in terms of a pair of vector fields E,B governed by Maxwell's equations. Further insight in the 20th. century lead to the ideas that, first, the equations could be formulated in a four-dimensional setting, with space and time on an equal footing, involving a single field tensor F. Second that this field has an essentially geometric origin. The geometry involves the introduction of a complex line bundle L over space-time, and the wave-functions of Quantum Theory are viewed as sections of L. Thus the value $\psi(x)$ of a wave function at a point is not naturally a complex number but lies in a onedimensional complex vector space Lx, and there is no completely canonical way to identify Lx with C. The basic geometrical structure is a connection on this line bundle and the field tensor F is the curvature of this connection. Mathematically, these ideas are underpinned by the general theory of bundles and connections which had been developed by differential geometers and which grow naturally out of classical differential geometry and notions such as the Gauss curvature. In Physics, these ideas lead to natural generalisations in "Gauge Theory" where one simply replaces the one dimensional vector spaces Lx by vector spaces of some fixed higher dimension. (The extension can also be formulated in the language of symmetry groups such as SU(2), SU(3).)

These general notions of bundles, connections and curvature can be formulated over manifolds of any dimension but there is a crucial special feature of 4-dimensions. The field tensor is a skew-symmetric tensor and in a four dimensionalspace, with a positive definite metric, these skew symmetric tensors decompose naturally into "self-dual" and "anti-self-dual" parts. So we can write $F = F+ +F-$ and we consider the special condition that $F+ = 0$. If we go back to make a "space-time decomposition" and express F in terms of a pair of vector E,B, this condition is just $E = B$, but the crucial thing is that the condition isactually a natural one in four-dimensions, independent of the decomposition.

Putting these ideas together, we see that if we consider a Riemannian metric on our 4-manifold M, a bundle E over M and a connection A on E, we can write down a natural condition

$$F+(A) = 0,$$

for the curvature tensor F(A). This is a partial differential equation for the connection A. If the dimension of the fibres of E is 1, as in electromagnetic theory, the equation is linear and we essentially recover part of the familiar Hodge Theory. But for higher dimensional fibres we get more subtle, nonlinear equations; the "Yang-Mills instanton equations". The basic strategy is to extract invariants of the manifold M from a study of the solutions (instantons) to these equations.

A variety of mathematical techniques are involved in extracting discrete invariants from the instantons. On the one hand there are fundamental analytical results of K. Uhlenbeck which give information about compactness of the space of solutions. A prerequisite here is the fact that the instanton equations are elliptic equations and roughly speaking Uhlenbeck's work allows the extension of standard ideas for linear elliptic equations to this nonlinear setting. On the other hand, there is a general and more abstract body of ideas which allowone to extend techniques of differential topology to certain infinite dimensional "Fredholm" problems. In particular, under suitable technical hypotheses, one gets discrete invariants from the solution spaces to the equations in much the same way as one can define the degree of a map $f : Sn \rightarrow Sn$ by "counting" (with signs) the points in a generic preimage $f-1(y)$ (i.e. by counting the solutions of the equation $f(x) = y$). Of course the crucial thing is that these discrete invariants are unchanged by continuous deformations of the data. This translates in our problem to independence of the choice of Riemannian metricon M.

The upshot of all this technical work was that one obtained, under suitable hypotheses, new invariants of M which took the form of a collection of polynomials functions on the homology group H2(M)[2]. The fact that we get a collection of polynomials comes from the fact that we have a choice of bundles E to consider. In the late 1980's these instanton invariants were used to give much new information about the "grand problem" above: for example by showing that certain large families of 4-manifolds with the same intersection form where all distinct up to diffeomorphism.

In 1994, Seiberg and Witten introduced some different equations in four dimensions, guided by considerations from Quantum Field Theory [7]. These share many of the features of the instanton equations, in that they are formulated in terms of a connection on a bundle over the 4-manifold, but now the bundle has fibre dimension 1, just as in electromagnetism. The new subtlety is that one considers a spinor field $\psi$ in addition to the connection on the bundle.This extra field can be thought of a something like the wave function of quantum mechanics but its' spinorial nature is crucial. The Seiberg-Witten equations take the shape

$$F+(A) = \psi\_\psi , DA\psi = 0,$$

where DA is the linear Dirac operator coupled to the connection and $\psi\_\psi$ denotes a certain quadratic form mapping spinors to self-dual 2-forms. Invariants of the underlying 4-manifold X can be extracted from the solutions to the Seiberg-Witten equations in a similar manner to the instanton case, but the newer theory has some decisive technical advantages. The invariants that result take the shape of certain distinguished classes ("basic classes") $\kappa i$ 2 H2(X) with associated integers ni. Witten made a wide ranging conjecture, backed up by almost overwhelming evidence from examples, as to precisely how these Seiberg-Witten invariants determine the polynomials given by the instanton theory. With these insights, the extent of the information which can be obtained from these methods has become much clearer, and the whole theory seems to have attained a reasonably mature form. (There is scope for exploiting the older instanton theory, and its relation with the Seiberg-Witten theory, particularly in applications of these ideas to 3-dimensions, as in recent work of Kronheimer and Mrowka [4], which establishes a result very like the Poincar´e conjecture for a slightly different class of 3-manifolds.)

### 4.2 Constructing diffeomorphisms

As we have emphasised in this article the problem of classifying manifolds has two complementary parts. In four dimensions we have now a good supply of invariants but what is almost entirely lacking is any way of constructing diffeomorphisms between manifolds, under suitable hypotheses on the invariants. We can write down many families of 4-manifolds with the same instanton and Seiberg-Witten invariants and we have no idea whether they are diffeomorphic or not. Something completely new is almost certainly needed to make substantial further headway with the "grand problem", but whether this will come in 1 year, 10 years or 100 years is anybody's guess. The only progress so far in this direction seems to lie in the special case of symplectic 4-manifolds. A symplectic structure on a 4-manifold is a closed 2-form ω which is everywhere nondegerate, a notable supply of examples being furnished by complex algebraic surfaces with Kahler metrics. Until the 1980's there were as many inaccessible questions about symplectic 4-manifolds as for the general case. But now we know a great deal more, principally through fundamental advances of Gromov and Taubes. These involve a network of ideas closely related to those above. In one direction, Gromov's fundamental paper [3] introduced the use of pseudoholomorphic curves as a tool to study symplectic manifolds. This development has had extremely wide-ranging consequences and uses some of the general ideas exploited in the instanton and Seiberg-Witten theories. One result of Gromov is particularly relevant to the classification problem because he shows that a symplectic 4-manifold satisfying suitable hypotheses, notably the existence of a certain kind of embedded 2-sphere, must be equivalent to the standard complex projective plane. The proof goes by moving the 2-sphere in a family of pseudoholomorphic curves sweeping out the manifold, and is quite parallel to arguments from the classification of algebraic surfaces. In the other direction, Taubes [6] discovered a fundamental connection between Gromov's pseudoholomorphic curves and the Seiberg-Witten equations and was able to use this to establish the existence of the required embedded sphere. Some of the author's recent work [1] has been motivated in part by the desire to extend this technique to more general 4-manifolds, but so far without very conclusive results.

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# Moduli of Vector Bundles

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## 1. Moduli problem for vector bundles.

The theory of moduli of (algebraic) vector bundles is an outgrowth of the classical theory of the Jacobian of an algebraic curve. The set of isomorphism classes of holomorphic (or algebraic) line bundles of degree *0* on a compact Riemann surface *X* has a natural structure of a smooth projective variety, the Jacobian of *X*. One may say that this variety solves the problem of moduli of line bundles on a smooth projective curve.

The corresponding moduli problem for (algebraic) vector bundles of higher rank on *X* was envisaged by A. Weil 1938 in a famous paper [19]. Naively formulated, the question is whether there is a natural structure of a variety on the set of isomorphism classes of algebraic vector bundles on *X* of a given rank and degree. However it turns out that one can expect a structure of a variety only on a suitable subset of the isomorphism classes of vector bundles.

## 2. Stable bundles and unitary bundles.

C. S. Seshadri and I were familiar with this paper of Weil already during our student days at the Tata Institute. Around 1961-62 we started thinking about the moduli problem for vector bundles on curves. Inspired by a remark in the paper of Weil, we first proved that the set of isomorphism classes of holomorphic vector bundles on *X*, which arise from irreducible unitary representations of the fundamentals group of *X*, has a natural structure of a complex manifold [15]. The proof used the then recently appeared work of Kodaira and Spencer. It also became clear to us that the basic problem was to give an algebraic characterization of holomorphic bundles arising from unitary representations of the fundamental group of *X*. Soon after doing this work, we became aware of David Mumford's talk at the 1962 International Congress of Mathematicians, in which he gave the definition of stable and semi-stable vector bundles on *X* and announced the result that the set of isomorphism classes of stable vector bundles of fixed rank and degree form a quasi-projective variety [8, 9]. Recall that a (holomorphic) vector bundle *V* on *X* is said to be stable (respectively semi-stable) if for every proper sub-bundle *W* of *V* we have

$$\frac{\deg W}{\text{rank } W} < \frac{\deg V}{\text{rank } V} \left(\text{resp. } \frac{\deg W}{\text{rank } W} \leq \frac{\deg V}{\text{rank } V}\right),$$

where deg $V = C_1(V)[X]$, $C_1(V)$ being the first chern class of *V*.

The remarkable similarities between stable bundles and bundles arising from irreducible unitary representations of the fundamental group (e.g. a unitary bundles is semi-stable, which was not difficult to see) led us to believe that the notion of stability would give an algebraic characteristation of unitary bundles.

Seshadri and I proved, the following:

**Theorem.** A holomorphic vector bundle on *X* of degree zero on *X* is stable if and only if it arises from an irreducible unitary representation of the fundamental group of *X* [16].

As a consequence one sees that a bundle arises from a unitary representation of the fundamental group if and only its indecomposable components are of degree zero and stable.

We also gave a characterization of stable bundles which are not necessarily of degree *0*, in terms of irreducible unitary representations of suitably defined Fuschian groups. This result implies that a set of isomorphism classes of stable bundles of rank *r* and degree *d* is a smooth projective variety if *r* and *d* are coprime.

The proof of the above theorem was based on the "continuity method" which is a general principle first proposed by Klein and Poincaré in the context of proving the uniformisation theorem for algebraic curves. Guided by this principle, we proved the theorem by showing

1) that the space of isomorphism classes of bundles arising from irreducible unitary representations of a given rank of the fundamental group (resp. stable bundles of degree *0* of the same rank) form a (Hausdorff) manifold $M_0$ (resp. $M_1$)

2) that $M_1$ is connected and $M_0$ is an open and closed subset of $M_1$.

## 3. The moduli space of semi-stable bundles.

The results stated above suggest a natural compactification of the space of stable bundles of degree *0*, namely the space of equivalence of classes of unitary representations (not necessarily irreducible) of a given rank. Seshadri proved that this compactification is a projective variety. Before stating his result precisely we will introduce an equivalence relation among semi-stable bundles.

Let $V$ be a semi-stable vector bundle on $X$. Then $V$ has a strictly decreasing filtration by sub bundles

$$V = V_0 \supset V_1 \supset \ldots \supset V_k = (0)$$

such that for $1 \leq$ i ( k the bundle Wi = Vi /Vi+1 is stable and satisfies □ EQ \F(deg Wi, rank Wi) □ = □ EQ \F(deg V, rank V) □ . Moreover the bundle Gr (V) = (ki=1 (Vi /Vi-l) s uniquely determined by V up to isomorphism (Jordan-Hölder theorem). We say that two semi-stable bundles V1 and V2 are S-equivalent if Gr(V1) is isomorphic to Gr (V2). Observe that two stable bundles are S-equivalent if and only if they are isomorphic. It is clear, using the theorem in the previous section, that the set of S-equivalence classes of unitary representations is in canonical bijective correspondence with the set of S-equivalence classes of semi stable vector bundles of degree 0.

C. S. Seshadri, using geometric invariant theory, proved the following:

**Theorem.** There is a unique structure of a normal projective (irreducible) variety
$U(r, d)$ on the set of *S*-equivalence classes of semi-stable vector bundles on $X$ of rank $r$ and degree $d$ such that the following property holds: if $\{V_t, t \in T\}$ is an algebraic family of semi-stable bundles on $X$ of rank $r$ and degree $d$ parametrised by an algebraic variety $T$, then the map $T \to U(r, d)$, sending $t \in T$ to the *S*-equivalence class of $V_t$ is a morphism [18].

We shall call the variety given by the above theorem, the moduli space of (semi-stable) vector bundles of rank $r$, and degree and denote it by $U(r, d)$.

The theorem stated above is also valid for a curve $X$ over an algebraically closed field of arbitrary characteristic.

## 4. Study of moduli spaces.

This work was followed by an extensive and deep study of these moduli space by S. Ramanan and myself. We first showed that that the smooth points of *U (r, d)* correspond precisely to stable bundles, except in the case of rank 2 bundles of even degree on a curve of genus 2; in this exceptional case the space is smooth [12]. We also determined explicitly the moduli spaces of rank 2 bundles in the case of curves of low genus. This work leads to surprising connections with classical algebraic geometry, like the theory of quadratic complex of lines, Kummer surfaces and the work of Coble on theta functions. For instance, by identifying the moduli space of rank 2 bundles with trivial determinant on a (non-hyperelliptic) curve of genus 3, with a quartic in $P^7$ considered by Coble, we were able to answer in the affirmative a question posed by Coble regarding the cubic equations defining a Kummer variety of dimension 3 [12, 14].

## 5. Moduli of curves and moduli of *S (r, d)*.

This section also describes some work done in collaboration with S. Ramanan. We will assume that *(r, d) =1.* We denote by *S (r, d)* the sub varity of *U (r, d)* corresponding to semi-stable bundles with a fixed line bundle as determinant.

**Theorem.** The (canonically polarized) intermediary Jacobian of *S (r, d)* corresponding to the third cohomology group is naturally isomorphic to the Jacobian of the curve *X* [13]. (For rank 2 bundles the result was first proved by D.Mumford and P. E. Newstead [10].)

As a consequence one sees that if $X_1$ and $X_2$ are two (projective, smooth) curves such that the corresponding moduli spaces $S_{X1}$ *(r, d)* and $S_{X2}$ *(r, d)* are isomorphic then $X_1$ and $X_2$ are isomorphic (This result was also proved by A. Tjurin).

The following result [13] implies that any small deformation of the moduli space $S_X$ *(r, d)* is of the form $S_{X_t}$ *(r, d)* where $X_t$ is deformation of the curve *X*.

**Theorem.** 1) The group of automorphisms of *S (r, d)* is finite and $H^i$ *(S (r, d), T)* $= 0$ for $i \neq 1$
where *T* is the tangent sheaf.

2) $\dim\ H^1 (S, (r, d), T) = (3g-3)$, where *g* is the genus of *X*.

In the course of these investigations we introduced and exploited systematically a certain correspondence between moduli spaces of vector bundles on a curve. This correspondence, which we called "Hecke correspondence", plays a significant role also in the study of Geometric Langlands theory.

## 6. Betti numbers of *S (r, d)*.

The Betti numbers of $S(r, d)$ were first calculated by P. E. Newsteasd in the case $r= 2$, $d =1$, by topological methods [17]. Based on these results G. Harder verified the Weil conjecture for $S(2, 1)$ in the case of a curve defined over a finite field, at a time when the Weil conjecture was not proved in general [4]. Harder observed in turn the Betti numbers of $S(2, 1)$ can be computed by arithmetical methods on the basis of the Weil conjecture.

Harder's method was generalized in a joint paper of Harder and myself, to bundles of arbitrary rank [5]. It was shown, in the case $(r, d) =1$, that the $\zeta$-function of $S(r, d)$ can be calculated from the $\zeta$- function on $X$. This result, together with the Weil conjecture proved by P. Deligne, gives a method for computing the Betti numbers of $S(r, d)$ when $(r, d) =1$.

We proved in this paper that an arbitrary vector bundle $E$ on acurve $X$ has a unique filtration by vector sub bundles

$$0 = F_0 \subset F_1 \subset \ldots \subset F_k = E$$

satisfying

a) $F_i / F_{i-1}$ is semi-stable for $i =1, \ldots, k$

b) $\mu (F_i / F_{i-1}) >( (Fi+1/ Fi )$  i =1, ... k-1

where for a vector bundle V (( 0) we put ( ( V) = deg V/rk V

This filtration, now called the Harder-Narasimhan filtration, and its generalizations play an important role in various contexts, including some in Number Theory.

## 7. Relationship with Physics: Gauge Theory and Conformal Field Theory.

Although I was attracted to the problems considered above entirely because of their intrinsic mathematical interest, it later emerged that these problems are intimately connected with Gauge Theory and

Conformal Field Theory, which play a significant role in mathematical physics. Some of my recent work was motivated and inspired by problems suggested by these areas of physics. In turn, physicists used in their work some of the results mentioned earlier.

Gauge Theory. An influential paper "Yang-Mills equations over Riemann surfaces" by M.F. Atiyah and R. Bott, which investigated moduli problems for vector bundles on Riemann surfaces from the point of view of gauge theory, appeared in 1982 [1]. This paper introduced the theory of vector bundles to a larger audience including physicists. Atiyah and Bott gave a new method for
computing the Betti numbers of the moduli spaces S (r, d), when (r, d) =1 and also proved that these spaces are torsion free.

Conformal Field Theory. Problems arising in Conformal Field Theory lead to studying linear systems on the moduli spaces S (r, d).Motivated by this, I studied first in collaboration with J.M. Drezet, the Picard group (of line bundles) on S (r, d) [3]. We proved that the moduli spaces are locally factorial and determined their Picard groups. This work enabled us to define generalized theta line bundles on these varieties and their sections are called generalized theta functions. (These bundles generalize the line bundles on the Jacobian determined by the Riemann Theta divisor and its multiples).

In conformal field theory one associates certain spaces of "Conformal Blocks" using representations of affine Kac-Moody algebras. In a joint work with S. Kumar and A. Ramanathan, I showed that the space of conformal blocks is isomorphic to the space of generalised theta functions, thus justifying in a rigorous way an important result of interest both to mathematicians and physicists [7]. [The result was also obtained by A. Beauville and Y. Laszlo)

Again suggested by results in Conformal Field Theory, a "Factorization theorem" was proved for generalized theta functions; this relates the vector space of generalized theta functions on the moduli space of vector bundles on a curve of genus g with the vector space of sections of certain generalized theta line bundles on the moduli spaces of (parabolic) bundles of curve of genus (g-1). In the case of rank 2 bundles this was proved by Ramadas and myself [11], while the higher rank case was treated by Xiatao Sun.

## 8. Generalisations.

The theory of vector bundles on curves has had considerable impact on other areas like Theoretical Physics, topology of 3-manifolds and Langlands Programme for function fields. The techniques of proofs in the theory have been drawn from Analysis, Differential Geometry. Algebraic Geometry, Number theory and Theoretical Physics.

In the case of higher dimensional algebraic varieties, the notion of stability depends on the choice of the cohomology class of an ample line bundle. The algebraic theory of stable bundles is fairly well developed and a nice exposition is given in [6].

There have been various deep generalisations, relating differential and algebraic geometry, of the theorem on stable and unitary bundles on curves. In the case of curves, one may mention the theory of Higgs bundles due to N. Hitchin. In the case of higher dimensional varieties, N.Hitchin and S.Kobayashi conjectured a generalisation relating stable bundles and Hermitian-Einstein metrics on holomorphic vector bundles. This conjecture was proved by S. K. Donaldson and also by S.T.Yau and K. Uhlenbeck. This generalisation plays a significant role in the profound work of S. Donaldson on the differential topology of 4-manifolds [2].

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