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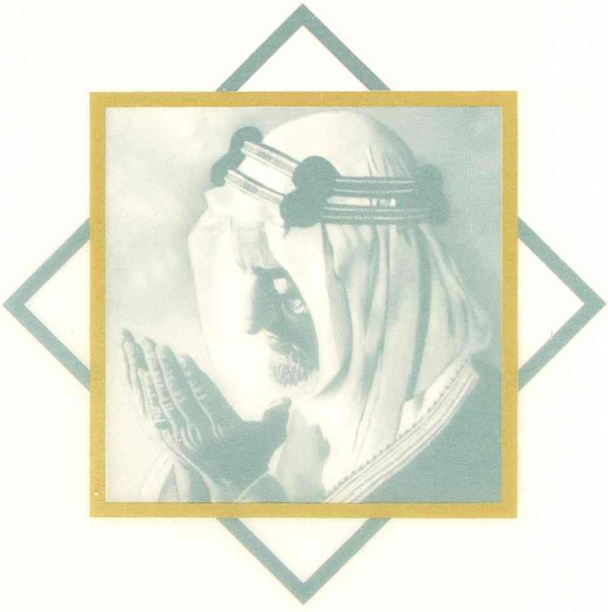
King Faisal International Prize

Articles In Medicine And Science III

THE 2002 KING FAISAL INTERNATIONAL PRIZE



ARTICLES IN MEDICINE AND SCIENCE III

THE 2002
KING FAISAL
INTERNATIONAL PRIZE

Custodian of the Two Holy Mosques

KING FAHD IBN 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 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 (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.

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 intemational referees. Autonomous, intemational specialist selection committees are then convened at the head-quarters 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)

2002 Prize Awards in Medicine and Science

The 2002 awards were presented in March 2002.

The Prize for Medicine (Pathophysiology of Chronic Heart Failure) was shared by Professor Finn Waagstein of Denmark and Professor Eugene Braunwald of USA.

Professor Finn Waagstein won the Prize in in recognition of his leading role in the development of beta-blockade treatment of congestive heart failure.

Professor Eugene Braunwald won the Prize in recognition of his outstanding contributions to understanding the pathophysiological mechanisms of congestive heart failure, and developing strategies for its treatment.

The Prize for Science (Mathematics) was shared by Professor Yuri I. Manin of Russia and Professor Peter Williston Shor of USA.

Professor Yuri I. Manin won the Prize in recognition of his fundamental contributions to the advancement of mathematics and modern mathematical physics.

Professor Peter Williston Shor won the Prize in recognition of his outstanding contributions to quantum computing, which prompted worldwide interest in the application of quantum mechanics in computer sciences.

N.B. The 2003 Prize topic for Medicine will be "Breast Cancer" and
The 2003 Prize topic for Science will be "Chemistry".

Winners Of The 2002
King Faisal International Prize
For Medicine

Medal: King Faisal International Prize for Medicine

Professor Finn Waagstein

Co-Winner of the 2002 King Faisal International Prize For Medicine

Professor Finn Waagstein receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier, Minister of Defence and Aviation
and Inspector General

(Center: HRH Prince Khaled Al-Faisal ibn Abd Al-Aziz)

SYNOPSIS OF ACHIEVMENTS

Professor Finn Waagstein initiated the brilliant concept of beta-blocking in the treatment of chronic heart failure due to dilated myocardiopathy. Despite earlier skepticism by the medical community, he pursued his belief in the beta blockers by conducting controlled clinical trials and pathophysiological studies that ultimatley led to the wide recognition of beta blockers as an important modality in heart failure treatment. He has also contributed to our understanding of autoimmune processes as an important factor in the development of dilated cardiomyopathy which is the major cause of heart failure in young and middle aged patients.

THE EVOLUTION OF THE BETA-BLOCKER TREATMENT CONCEPT IN CONGESTIVE HEART FAILURE

FINN WAAGSTEIN

Professor of Cardiology and Senior Physician,
Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska University Hospital,
Gothenberg University, Sweden

Background

In the early 1970's congestive heart failure, with the exception of heart failure due to valvular disease, was generally considered to be a lethal disease with limited prospects of cure. The only drugs available were diuretics and digoxin which ameliorate symptoms but do not prevent ongoing deterioration of heart function. It was believed that the underlying destruction of cardiac tissue would not allow for recovery of heart function and would inevitably lead to untimely death.

This was however not always the case. Recovery of heart failure could be seen when patients abusing alcohol have stopped drinking. Furthermore, patients with heart failure related to bacterial and virus infections, whether this was the direct cause of the heart disease with inflammation in the heart muscle or a complicating factor to a pre-existing heart disease, could recover completely when infection was abolished.

Finally patients with persistent fast heart rate due to arrhythmias who developed a condition with increased heart size and poor pump function could achieve complete recovery when heart rate was normalized with drugs or surgical intervention.

In animal experiments we showed that long-term administration of noradrenaline, a stress hormone, could produce heart failure which also could be seen when heart rate was increased by pacing. Humans and experimental animals with end stage heart failure have very little stress hormone left in the heart tissue and complete blocking of the effect of these stress hormones in patients and animals with severe heart failure with beta~blockers caused severe

deterioration of heart function. It was therefore thought that an appropriate treatment should be to treat with stress hormone-like drugs to improve heart function and ameliorate heart failure symptoms.

For many years this was therefore the prevailing treatment approach among majority of cardiologists. However, despite short-term improvement of heart function there were no long-term improvement and all controlled trials with drugs which stimulate heart function have shown increased mortality.

American heart researchers showed as early as 1965 that energy production was compromised in the heart muscle in heart failure and among some of these researchers there were speculations whether it was a clever strategy to increase the energy requirement in the heart muscle further by stimulating the heart because an increase in energy deficit may lead to further damage to the heart muscle causing cell death.

In the early 1970's we observed that many patients with acute myocardial infarction had elevated stress hormones in the blood which increased both heart rate and blood pressure thereby causing energy imbalance in the heart muscle leading to extension of the infarct. Intravenous administration of a beta-blocker caused often marked relief of chest pain and the drug was extremely well tolerated even in case of signs of acute heart failure which occurred in approximately 1/5 of the patients in our studies.

Beta-blockade caused an immediate decrease in blood pressure and heart rate thereby reducing the energy requirement in the heart muscle which prevented destruction of heart muscle tissue. It was later shown by direct measurement of heart function that beta-blockers did not cause deterioration, and the size of the infarct became smaller and the risk of dying over the following year was reduced by 50% in the subset of patients who showed signs of acute heart failure before they were given beta-blockers. The most impressive effect was seen by early beta-blocker treatment in those patients showing clear cut signs of acute heart failure.

Clinical observations in chronic heart failure

The observations from the use of beta-blockers in acute myocardial infarction with acute heart failure led us to the following hypothesis: If a patient with chronic heart failure had increased heart rate, could this be a sign of increased influence of stress hormone? Energy production was already compromised

because of reduced fatty acid oxidation which is the most important contribution to energy production in the heart muscle. What would happen if beta-blockers were given cautiously, initially in low doses, with slow increment in doses over several weeks? Our first patient was a 58 year old woman with a 6 years history of progressive heart failure due to dilated cardiomyopathy, a primary heart muscle disease. She had marked increase in heart rate. Having been hospitalized for total 7 months over the last 12 months she had an almost complete recovery after a year without any new hospitalizations. She survived another 24 years until the age of 82. This case was published together with 6 more cases having a similar dramatic improvement after beta-blocker treatment. To prove that it was not a spontaneous improvement, which sometimes can be seen in dilated cardiomyopathy, we withdraw beta-blocker treatment from a number of patients who have improved on beta-blockers. Withdrawal of beta-blockers was found to lead invariably to deterioration of heart function. After reinstitution of beta-blocker treatment improvement was observed again. For us it was convincing proof that beta-blockade in heart failure was beneficial. However, two research groups in Australia and New Zealand performed short-term placebo controlled studies with beta-blockers which failed to show improvement. The duration of these studies was, however, only 4 weeks which according to our preliminary studies was too short to obtain improvement. Improvement could only be seen after at least 3 months treatment. As a consequence the beta-blocker concept was not accepted by the cardiology community. Another reason for not accepting beta-blockers for heart failure was lack of obvious rationale for the treatment concept. Our understanding of the mechanisms for development of heart failure was rudimentary at that time.

We were still waiting for the neuroendocrine concept to explain why patients with heart failure continue to deteriorate under the influence of the strong neuroendocrine activity in heart failure. Furthermore, most researchers dealing with heart failure patients believed that inotropic drugs should be used to stimulate heart function rather than depressing heart function with a beta-blocker.

After a delay of 10 years some sporadic reports from a few American centers appeared which confirmed our original findings. By co-working with these centers in a placebo-controlled Multicenter approach we succeeded finally in 1993 to show that the beta-blocker metoprolol improved cardiac function, exercise capacity and quality of life and reduced hospitalization for heart failure and the need for cardiac transplantation.

Rationale for the use of beta-blockers in heart failure

Meanwhile we confirmed that patients with heart failure had energy imbalance which was normalized after long-term beta-blocker treatment. Efficiency of the heart muscle was dramatically improved by up to 100% after long-term treatment. This implies that more mechanical work could be performed without increased energy cost. We found that the heart became smaller, congestion in the lungs was reduced and the heart muscle could pump more blood per beat. These findings could explain why deterioration of heart function was slowed down. In fact patients may remain stable over many years in contrast to patients not treated with beta-blockers who continued to deteriorate. We also found that the increased stimulatory activity through sympathetic nerves was reduced, not only to the heart, but also to the kidneys and muscles. We also saw enhancement of the parasympathetic nerve activity. These two changes resulted in lower resting heart rate and improved electrical stability which can explain the dramatic reduction in the risk of sudden cardiac death in the large beta-blocker trials.

Recently it has been shown that beta-blockade also diminishes the activity of the renin-angiotensin system, reduces synthesis and release of endothelin, reduces oxidative stress and programmed cell death and interacts with the immune system possibly by blocking circulating cardiac autoantibodies directed against beta-receptors. Such antibodies have been shown experimentally to induce heart failure. It is therefore probable that beta-blockers have many other positive effects in heart failure apart from reducing heart rate and improving energy balance. Recently we have finally proven our original hypothesis in experiments in rats with heart failure that long-term beta-blockade can completely normalize energy deficit and improve heart function. Indirectly we have also shown in humans that fatty oxidation is normalized after long-term beta-blockade.

Multicenter trials with beta-blockers in heart failure

Final acceptance of new treatment modalities can only be achieved after showing in a placebo-controlled trial that death rate and hospitalization rate could be reduced without causing harm to any specific group. This requires a great number of patients and was accomplished in 1999 and 2001 in three large trials with 3 different beta-blockers showing almost exactly the same reduction in mortality and good tolerability. It is somewhat frustrating that the original observation of beneficial effects of beta-blockers in heart failure should take 25 years to be generally accepted and will take another 5 to 10 years to be

completely implemented by the medical profession. It is estimated that adding beta-blockers to conventional treatment of heart failure during the last 25 years would have increased life expectancy by at least four years with improved quality of life for 25 million patients in the industrialized world with 1.2 billion inhabitants who can afford to pay for heart failure treatment and even more if we include all patients suffering from heart failure. Several papers have shown improved cost benefit since beta-blockers in addition to prolonging life also keep the patients out of hospital. It is estimated that the doubling of death due to heart failure during the last 17 years might have been prevented by a widespread use of beta-blockers for this condition.

To conclude it is quite obvious that beta-blockers are the most effective group of drugs for treatment of heart failure and should be given as soon as the diagnosis of heart failure is established.

Other contributions in heart research

Clinical studies

Alternative treatment for angina pectoris

I have been mentor of a research group that developed a device for electrical stimulation of the spinal cord in patients with intractable angina pectoris due to coronary artery disease and angina pectoris with normal coronary arteries. This device has been shown not only to decrease the number of pain episodes and severity of pain but also the degree of ischemia indicated by lower production of lactate from the heart muscle and less electrocardiographic changes indicating ischemia. The device can be administrated by the patient himself both for prevention of angina and to treat acute episodes of angina. The effect of the device is additive to pharmacological treatment and has been used widely in Scandinavia in patients with recurrent angina after repeated surgical treatment and in patients who are at too high α risk for heart surgery.

Exploring causes for dilated cardiomyopathy

Patients with dilated cardiomyopathy have circulating auto-antibodies directed against the beta-receptors in the heart muscle cell. We have shown that these antibodies act in a similar way as stress hormones by binding to the receptor increasing heart rate and the strength of muscle cell contraction. In the long

perspective this may lead to exhaustion of energy reserve in the heart muscle, resulting in decreased function and cell death. Experiments have shown that introducing these auto-antibodies in rabbits leads to development of dilated cardiomyopathy which can be prevented by beta-blockers. These observations may explain the very beneficial effect of beta-blockers in these patients. Additional support for this hypothesis is the marked improvement which can be seen in these patients when the auto-antibodies are removed by immunadsorption. A large controlled study is now in progress to verify these observations with the hope that we can prevent these patients from heart transplantation or artificial hearts.

Coronary artery disease in heart transplanted patients

In heart transplant patients we have found that patients who had coronary artery disease as the cause of heart failure leading to transplantation the risk is many fold higher to develop coronary artery disease in the transplanted heart compared to patients transplanted due to heart failure caused by heart muscle disease despite similar risk factor profile after transplantation. These findings may lead to a better understanding of mechanisms for development of atherosclerosis.

Cardiac protection in cancer treatment

It is established that as many as 10% of all patients treated for lymphatic cancer and leukemia have signs of compromised heart function during long-term follow up. In some instances this may lead to severe heart failure requiring heart transplantation. Fortunately, these patients respond to some degree to beta-blockade. We have recently confirmed that adolescents who have undergone treatment for childhood leukemia invariably have decreased cardiac functional capacity during exercise. Our aim to establish methods which protect the heart muscle during cancer treatment has therefore high priority in our research over the next five years.

Experimental studies

Studies on heart muscle metabolism

During the last decade we have established experimental facilities for cardiac metabolic research using magnetic resonance spectroscopy in the intact animal which have increased our understanding of the underlying disturbances in energy metabolism in heart failure. We have found that early treatment with growth hormone in rats with heart failure after myocardial infarction restores energy balance in the heart muscle and prevents the heart from increasing in size and inhibits heart failure progress. These findings require more studies and if these changes are sustained after long-term follow up they may lead to a new treatment concept for patients with acute myocardial infarction. We have also confirmed that beta-blockers in a heart failure model normalize myocardial energy metabolism. These types of studies are important because we hypothesize that new drugs which improve function also must show beneficial effect on energy metabolism in the heart muscle. This has not always been the case in the past since many drugs which stimulate the heart muscle also increase energy demand in an already disturbed metabolism which could lead to increased heart muscle cell death and life-threatening rhythm disturbances. Other studies in progress are methods to protect the heart muscle against cancer drugs used for lymphatic cancer and breast cancer. There are several candidate drugs which must be further investigated in animal models. Since the damage from the cancer drugs hits the mitochondrium predominantly, which is responsible for energy production, our magnetic resonance spectroscopy methods are appropriate for this: purpose.

Studies on cardiac auto-antibodies

In order to further investigate the etiology of dilated cardiomyopathy we have shown that transfer of lymphocytes to mice from humans with dilated cardiomyopathy and auto-antibodies against beta-receptors causes cardiomyopathy.

Summary

My research has been focused on definition and implementation of a new treatment concept for heart failure. It has been somehow frustrating to have proposed the use of beta-blockers at such an early stage before cardiologists were ready to accept such a controversial concept. Time is however, mature now and the positive response during the last few years have been overwhelming. From this starting-point further interest has been focused on understanding the rationale for beta-blocker treatment particularly with reference to energy metabolism in the heart muscle which seems to be important also when other drugs are investigated. Being responsible for setting up a heart transplant clinic and seeing many young people suffering from dilated cardiomyopathy the interest has also been focused on understanding the etiology of primary heart muscle disease which causes approximately 20% of all heart failure cases. To go further in this direction a bench to bedside approach is required to understand mechanisms and implement our knowledge into clinical practice.

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PROFESSOR EUGENE BRAUNWALD

Co-Winner of the 2002 King Faisal International Prize For Medicine

Professor Eugene Braunwald receives his prize from
HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier, Minister of Defence and Aviation
and Inspector General

(Center: HRH Prince Khaled Al-Faisal ibn Abd Al-Aziz)

SYNOPSIS OF ACHIEVEMENTS

Professor Eugene Braunwald s distinguished career over 40 years places him at the forefront of the investigators of congestive heart failure and the acute coronary syndromes. His remarkable track of achievements includes the development of several novel pathophysiological concepts, all of which have had, or are likely to have, a significant impact on treatment of congestive heart failure. His studies on the imbalances of the sympathoadrenal system have been the prelude to the recent advances with the use of beta-adrenergic blocking drugs. His leadership of the multinational TIMI (Thrombolysis In Myocardial Infarction) trials since 1984 have led to refining the optimal strategies to promote preservation of myocardium and to salvage heart muscle cells.

Professor Braunwald is the author of more than 1,100 publications, an editor of *Harrison s Principles of Internal Medicine* (Editor-in-Chief of the 11th edition and the current 15th edition) and the founding editor/author of *Heart Disease*, now in its 6th edition. These two books are the leading texts in internal medicine and cardiology respectively.

CONGESTIVE HEART FAILURE
Five Decades of Progress

EUGENE BRAUNWALD

Distinguished Hersey Professor of Medicine at Harvard Medical School and
Faculty Dean and Chief Academic Officer of the Partner Health Care System founded by
assachusetts General Hospitals

My first intensive contact with patients suffering from congestive heart failure occurred in 1952, just a half century ago. As a medical student at New York University I was assigned to a heart failure clinic, one of the first devoted entirely to patients with this condition, and a hemodynamic laboratory under the leadership of Professor Ludwig W. Eichna, a pioneer clinical investigator of heart failure. The patients with heart failure whom I encountered usually had hypertension or rheumatic valvular disease (Table 1). The suggested underlying mechanism - "exhaustion of the overloaded ventricle" - had not changed since it had been proposed by Osler more than a half century earlier .

Treatment with bed rest, digitalis, salt free diet, and intramuscular merculydrin was applied, more or less indiscriminately to all patients, and also had not changed for several decades. My subsequent interest in heart failure has been in three principal areas:

NEUROHORMONAL DISTURBANCES

In the early 1960s my colleagues and I described the first neurohormonal disturbance in heart failure. We reported that circulating concentrations of the adrenergic neurotransmitter, norepinephrine, were abnormally elevated in patients with heart failure, particularly during exercise. This was associated with elevations in the quantity of norepinephrine excreted in the urine, and with marked reductions in the cardiac content of the neurotransmitter. Much has been learned about abnormalities in adrenergic signaling in the last four decades. Most important, from a clinical perspective, has been the realization that the hyperadrenergic state characteristic of heart failure can, on a chronic basis, impair cardiac function further, and that beta-adrenergic blockade prolongs life and reduces hospitalizations for heart failure in a large proportion of patients with systolic heart failure.

The second humoral system in heart failure which I investigated was the renin-angiotensin-aldosterone system. With the Drs. Pfeffer we found that angiotensin converting enzyme inhibition (ACEI) prevents hypertrophy and left ventricular dysfunction in spontaneously hypertensive rats, and prevents left ventricular dilatation and death in rats with myocardial infarction. The salutary hemodynamic effect was also observed in patients with myocardial infarction. These observations culminated in the SAVE trial, which was the first trial to demonstrate an improvement of survival in patients post-infarction who had left ventricular dysfunction without overt heart failure. Just as was the case for beta-blockade, ACEI has been shown to prolong life in a large proportion of patients with heart failure, and has become a cornerstone in the treatment of this condition.

The entire field of neurohormonal disturbances in heart failure has moved forward rapidly, and a variety of other blockers appear to be beneficial in the treatment of heart failure. These include angiotensin receptor II blockers, endothelin blockers as well as blockers of the neural endopeptidase that catalyzes the breakdown of atrial natriuretic peptide. In experimental heart failure preparations, blockers of arginine vasopressin and of a number of cytokines, especially tumor necrosis factor α also appear to be salutary.

DISTURBANCES OF MYOCARDIAL FUNCTION

In the 1960s there was still considerable controversy regarding the intrinsic function of the myocardium in heart failure. We created two models of heart failure. In papillary muscles removed from kittens with obstruction to right ventricular outflow and studied in vitro, we observed a marked disturbance of force development and velocity of contraction. We created a second model of heart failure by causing prolonged tachycardia induced by several weeks of ventricular pacing and observed that when the pacing was discontinued the hemodynamic changes characteristic of heart failure, including reductions of stroke volume and ejection fraction persisted.

Since these early studies our understanding of disorders of contractile function in heart failure has advanced considerably. Disturbances in myocyte shape and dimensions have been reported and contractile defects at the sarcomeric level have been observed in human (as well as animal) cardiac muscle in heart failure. Moreover, it has been observed that with prolonged unloading of the heart with a left ventricular assist device. normal myocardial function may be restored in some patients.

MYOCARDIAL ENERGETICS

Table 2 shows six postulated pathogenetic mechanisms for the development of heart failure. I have been particularly interested in the fourth of these, i.e. a reduction of the availability of high energy phosphate stores. In both of the aforementioned models of heart failure - the kitten with chronic right ventricular pressure overload as well as in the dog with pacing induced tachycardia, the total stores of high energy phosphates and the ratio of creatine phosphate to adenosine triphosphate were found to be reduced. Since then such reductions have been described in patients with heart failure secondary to mitral regurgitation and dilated cardiomyopathy. The lack of energy stores appears to play a role in the pathogenesis of heart failure in conditions other than coronary obstruction. However, in 1982 we postulated that in the latter condition, heart failure may be caused by chronic stunning, i.e. repetitive episodes of myocardial ischemia not severe enough to cause myocardial necrosis. Chronic stunning can lead to ischemic cardiomyopathy, a very common form of heart failure which may not be associated with signs of overt ischemia, such as angina or electrocardiographic changes. When this condition is recognized it may be treated successfully by coronary revascularization. Indeed, revascularization of ischemic cardiomyopathy is now the most common method of permanently reversing heart failure.

CONCLUSIONS

It has been my good fortune in the last half century to witness, often at close range, many important developments in heart failure and to participate in several of them. The view of the condition has changed enormously in the past fifty years (Table 3). While there has been substantial progress in management, both the incidence and prevalence of heart failure are increasing rapidly, in large part because of the progressive aging of the population. However, there now exist several areas of special opportunity (Table 4). These include the prevention of heart failure - by preventing its most common cause - ischemic heart disease. Several new areas of therapy, including newer blockers of neurohumoral and cytokine causes of cardiac damage appear promising. Sudden cardiac death, responsible for about half of the mortality of heart failure can be largely prevented by the implantation of internal cardioverter defibrillators. Cardiac replacement with a totally implanted artificial heart or by xenotransplantation is undergoing rapid development. Finally, I believe that myocardial regeneration, using stem cell based therapy, holds out the greatest promise.

Table 1

Heart Failure in 1951

Etiologies	Hypertension, Valvular HD
Mechanism	"Exhaustion" of Overloaded Ventricle
Goals of Rx	Reduce symptoms by ↓ fluid accumulation, Improve hemodynamics
Management	Similar therapy for all Digitalis Bed rest Strict Na+ restriction Mercurial diuretics I.V. catecholamines for acute pump failure
Attitude	Hopelessness

Table 2

MECHANISMS OF HEART FAILURE – 2001

- Reinduction of fetal expression of sarcomeric proteins
- Myocyte Ca^{2+} overload
- Myocyte apoptosis
- Abnormalities of cytoskeletal proteins
- Impaired energy metabolism (including chronic stunning)
- Interstitial fibrosis

Table 3 top

CHANGES IN FOCUS ON HEART FAILURE

	1951	2001
Etiologies	Hypertension Valvular Hd	Ischemic HD Cardiomyopathies
Mechanisms	"Exhaustion" of overloaded ventricle	Molecular mechanisms Abnormal gene expression
Goals of Rx	Reduce symptoms by: ↓ fluid accumulation ↑ contractility ↓ vent. Rate in AF	Improve quality and duration of life Prevent deterioration of pump function Prevent fatal arrhythmias Shorten hospitalization

Table 3 bottom

Management	Similar therapy for all Digitalis Bed rest	Individualized therapy Aggressive management plan, close followup in HFcenters
	Na+ restriction Mercurial diuretics	ACE inhibitors, β blockers, loop diuretics, moderate exercise Spironolactone, digitalis, Anticoagulants
		LVAD, ICD, Transplantation
Encouraging Experimental Therapies	I.V. catecholamines for acute pump failure	AT_1 receptor blockers, endothelin blockers, TNF I blockers Vasopeptidase inhibitors
Attitude	Hopelessness	Guarded optimism

Modified from: Eur. Heart J. Vol. 22, 2001, pp. 825-836

Table 4

HEART FAILURE: Future Directions

- Greater application of established therapies
- Additional blockade of activated neurohormonal/cytokine systems
- Prevention of HF through genetically-targeted prevention of ASCVD
- Prevention of sudden cardiac death
- Prolonged mechanical unloading
- Cardiac replacement: artificial ht., xeno-transplantation
- Myocardial cell replacement

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Winners Of The 2002
King Faisal International Prize
For Science

Medal: King Faisal International Prize for Science

PROFESSOR YURI I. MANIN

Co-Winner of the 2002 King Faisal
International Prize For Science

SYNOPSIS OF ACHIEVEMENTS

Professor Yuri Manin is one of the most influential mathematicians of the 20th century. He has made fundamental contributions to mathematics and modern physics. Among his earlier achievements in algebraic geometry were proof of the Mordel Conjecture, which led to the introduction of the Gauss-Manin Connection, a vital tool in modern algebraic geometry, and disproof of the Luroth problem (jointly with Iskovskih). In the number theory, Professor Manin discovered certain constraints (called the Brauer-Manin Obstruction) to the existence of rational solutions of Diophantine equations; these are algebraic equations for which integer solutions are sought. He also launched a program of studying algebraic manifolds with many rational points. An algebraic manifold is a surface that is locally described around each point by a family of algebraic equations. Professor Manin and his students also did widely recognized work on error correcting codes algorithms used to detect and correct any error based on the remaining members in a sequence of numbers.

From the late 1970s, Professor Manin turned to the application of ideas from algebraic geometry to mathematical physics: quantum field theory and quantum strings. Jointly with Atiya, Drinfeld, and Hitchin, a description (the ADHM construction) was given for all solutions to the Yang-Mills equations on a four-dimensional sphere; these solutions are interpreted in physics as instantons (particle-like wave packets that occupy a small region of space and exist for an instant of time). Recognition of certain spaces in algebraic curves led Professor Manin to the calculation of the string measure. Strings in physics are one-dimensional objects that are believed to constitute the fundamental building blocks of matter. The work of Professor Manin was an important step in furthering research into the string theory.

His contributions to quantum, or non-commutative geometry, are also well known, particularly a basic construction known as the Manin plane. More recently, he contributed to the development of a mathematical theory of quantum cohomology which, in broad terms, is a methodology for studying non-commutative geometry using algebraic tools.

SUMMARY
OF THE MAIN SCIENTIFIC RESULTS OF

YURI I. MANIN

Director, Max-Planck-Institute for Mathematics, Bonn, Germany,
Board of Trustees Professor, Northwestern University, Evanston, USA and
Leading Researcher , Steklov Mathematical Institute, Academy of Sciences,
Moscow, Russia

The main themes of the mathematical reseaxch of Yuri Manin can be summarized as follows: Geometry, especially Algebraic Geometry, and geometric thinking, as the unifying and creative principle in Number Theory, Physics and Computer Science. They are presented below in the thematic and roughly chronological order.

1. Algebraic Geometry

Proof of the Mordell Conjecture over fields of functions. The Mordell Conjecture expresses the basic qualitative relation between the topological and the arithmetical properties of one-dimensional algebraic varieties (curves): if the genus (number of handles) is > 1, the number of rational points is finite. Yuri Manin proved this Conjecture in 1963 for the case when the curve in question is defined over a field of functions, that is, depends on parameters. The main technical tool introduced in this proof is now called "the Gauss-Manin connection" and constitutes one of the most widely used basic constructions of Algebraic Geometry.

Disproof of the Lüroth Conjecture. Lüroth's Theorem says that any nontrivial subfield of the field of rational functions of one variable $C(\chi)$ is generated by one function $t = t(\chi)$. Similarly, any subfield of $C(\chi,\gamma)$ is generated by one or two independent functions. Yuri Manin proved in 1971, in collaboration with V.A. Iskovskih, that for three variables this is not true any more. The method developed in their paper was based on a deep and technically sophisticated study of birational transformations. It led to the creation of a whole new chapter of Algebraic Geometry studying birational rigidity of Fano manifolds.

2. Number Theory: Diophantine Equations

Brauer-Manin obstruction. In the theory of Diophantine Equations, *i.* e. polynomial equations with integral coefficients, one of the. first questions is: how to establish that an integral solution exists or otherwise, if no explicit solution is known? Indirect methods of provhlg unsolvsbility are generally called "obstructions". If the method fails, one says that the respective obstruction "vanishes".

A classical obstruction (going back to Gauss) is this: weaken the equation to a congruence modulo some *N;* if the congruence is unsolvable, the equation is unsolvable as well. The "first obstruction" is well amenable to both algorithmic (say, computer assisted) computation and to the theoretical study. The Minkowski-Hasse principle states that for quadratic forms, if the first obstruction vanishes, the equation is always solvable. Examples show that starting with degree 3, the vanishing of the first obstruction does not imply the solvability.

In his talk at the International Congress of Mathematicians in 1971, Yuri Manin proposed the second obstruction, based upon the Brauer group of the respective equation (or manifold). It might be non-trivial even when the first obstruction vanishes. This remains the only known general new obstruction in Diophantine Geometry. Considerable amount of work were dedicated to the proof of the solvability of various classes of equations in the case of vanishing of this obstruction.

Research Program: Manifolds with many Rational Points; Manin's Linear Growth Conjecture. Mordell Conjecture is an instance of the general principle which is expected to be valid in Diophantine Geometry: if the canonical class is ample (manifolds of general type, "negative curvature, hyperbolicity"), the manifold must have few rational points in the sense that they must lie on submanifolds of lesser dimension.

To the contrary, when the anticanonical class is ample (Fano manifolds, "positive curvature, ellipticity"), one expects it generally to have many rational points.

In the end of the eighties, Yuri Manin launched a research program aimed at studying manifolds with many points quantitatively. The main notions, available tools, and conjectures were expounded in his joint paper with V. Batyrev in 1990. Two general new phenomena were discovered: a) existence of the

"accumulating subvarieties" concentrating anomalously many points; b) linear growth of the number of points of bounded anticanonical height on the complement to all accumulating subvarieties.

A couple of international conferences were dedicated to the developments connected with this project.

3. Number Theory: Modular Forms and Zeta Functions

Modular forms belong to the central notions of Number Theory. Their Fourier coefficients are interesting number-theoretical functions like numbers of solutions of Diophantine equations and congruences. Their Mellin transforms are the L-series encoding the arithmetics of the representations of the Galois group in the (non-)commutative class field theory (Langlands program). Finally, from the geometric viewpoint, they are differential forms on various moduli spaces.

In the series of works published in the seventies, Yuri Manin created the basics of the theory of modular symbols and p-adic L-series related to the modular forms. His plenary talk at the International Congress of Mathematicians in 1978 was dedicated to this theory.

4. Mathematical Physics: String Theory and Quantum Cohomology

Contemporary theoretical physics to a large degree is the theory of quantum strings and their multidimensional generalizations, "branes". These multidimensional structures replaced the classical paradigm of an elementary particle as a point object, and its quantized versions.

The new physics is a highly mathematicized endeavor, in which algebraic geometric methods play the far more prominent role, than, say, functional analysis and representation theory that constituted the mathematical tools of the preceding historical phase. During the last two decades, Yuri Manin dedicated many publications to the various aspects of this vast subject.

Computation of the Polyakov measure in the theory of bosonic strings. After the theory of instantons (see below), this computation published by Yuri Manin in

1986, was the first breakthrough of Algebraic Geometry in String Theory. Moduli spaces of algebraic curves, introduced by Riemann and thoroughly studied on their own only in the sixties, entered in the mathematical physics.

Quantum Cahomology. The theory of quantum strings propagating in a space-time with non-trivial topology led in the nineties to the development of a new mathematical theory, Quantum Cohomology. The first notions of this geometric theory are due to the physicists E. Wit ten and C. Vafa. Its mathematical foundations in the :framework of Algebraic Geometry (as opposed to the Symplectic Geometry) were laid down in the paper by M. Kontsevich and Yuri Manin in 1994, and extended in the papers by Yuri Manin and K. Behrend. Yuri Manin's monograph published in 1999, summarizes the first decade of the development of this rich theory.

The name of the Quantum Cohomology is explained thus: one of the main new constructions is the deformation of the classical cohomology ring: instead of counting only intersection points of cycles, as the usual theory, one starts counting, with weights, points connected by algebraic curves passing through them.

To make the prescription of such counting precise, one has to use the most sophisticated tools of the Algebraic Geometry, developed in the preceding decades: intersection theory of stacks and derived categories. As a reward, one gets a theory which not only has a great potential for explaining the properties of the matter and space-time at very high energies, but has great intrinsic mathematical novelty, beauty and coherente. In particular, the completely unexpected mathematical fact was discovered: all cohomology classes of moduli spaces of algebraic curves with marked points, act as polylinear operations upon cohomology of all smooth projective varieties.

5. Mathematical Physics: Instantons, Quantum Groups, Integrable Systems, Supersymmetry

Instantons. Yuri Manin together with V. Drinfeld produced the classification of self-dual solutions of Yang-Mills equations (instantons). This solution, discovered simultaneously and independently by M. Atiyah and N. Hitchin, was published in a famous 1978 paper signed by all four authors and became known as the AHDM construction. The theory of instantons, developed further by S.

Donaldson, acquired a central role in the four-and three-dimensional differential geometry.

Quantum Groups. The foundations of the theory of Quantum Groups were developed by Yuri Manin's student V. Drinfeld, which earned him Fields Medal. Yuri Manin developed a different approach to Quantum Groups as symmetry objects, which became quite popular in theoretical physics. The simplest quanturn group $GL_q(2)$ is the symmetry group of "Manin's plane" with coordinates χ,γ satisfying $\chi\gamma = q\gamma\chi$, exactly in the same way as the usual $GL(2)$ *is* the automorphism group of the usual plane.

Integrable Systems. In this domain, Yuri Manin discovered and studied (with B. Kupershmidt and D. Lebedev) the hierarchy of higher hydrodynamic equations of Benney's type. He found (with A. Radul) a supersymmetric extension of the KdV hierarchy. Finally, he introduced the non-commutative residue or the one-dimensional pseudodifferential operators. Generalized by M. Wodzicki to the multidimensional case, this proved to be an important tool in Non-Commutative Geometry.

Supersymmetry. In the course of studying the supergravity and the supersymmetric Yang-Mills equations, Yuri Manin produced the exposition of the mathematical notions of supergeometry (geometry with commuting and anticommuting coordinates) which set the standard in this domain: see his monograph "Gauge Fields and Complex Geometry" published by Springer in 1988, and re-edited with complements in 1997.

6. Computer Science: Error-Correcting Codes, Quantum Computing

Error-Correcting Codes. Yuri Manin's work on the Goppa codes was produced in the framework of his seminar on applied algebra. It led to the general formulation of codes of algebro-geometric type. This theory was first presented in the 1985 paper by Yuri Manin and his student S. Vladuts, and in the paper by M. Tafasman, S. Vladuts, and Th. Zink, stemming from the same seminar, it was demonstrated that there exist asymptotically very good Goppa codes admitting polynomial encoding/decoding algorithms. This pioneering work determined the development of the theory of error-correcting codes for two decades.

Quanturn Computing. Quantum Computing is the recent theoretical development in Computer Science that paves the ground for the creation of the next generation of computers, whose processors are expected to be fundamentally quantum devices, exploiting quantum superposition for implementing massive parallel computation.

Yuri Manin proposed the development of the theory of quantum computers in his book "Computable and Uncomputable" published in 1980. This suggestion was based on the analysis of the capacity of information storing of quantum systems. The same idea, with basically the same arguments, was independently developed in a talk by Richard Feynman in 1982.

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PROFESSOR PETER WILLISTON SHOR

Co-Winner of the 2002 King Faisal International Prize For Science

Professor Peter Williston Shor receives his prize from HRH Prince Sultan ibn Abd Al-Aziz, Second Deputy Premier, Minister of Defence and Aviation and Inspector General

(Center: HRH Prince Khaled Al-Faisal ibn Abd Al-Aziz)

SYNOPSIS OF ACHIEVEMENTS

Professor Peter Shor is best known for discovering the first interesting application of quantum computers, hypothetical machines of which only small prototypes have been built to date. He showed that quantum computers could factor large integers into primes and compute discrete logarithms much faster than the algorithms used on digital computers. Shor's algorithms use a number of steps that grows only polynomially in the size of the instance, for example, the number of digits in the number to be factored. Shor then made the physical development of quantum computers seem much more feasible by showing that errors in the computation need not inevitably disrupt the operations of a quantum computer; he exhibited quantum error correcting codes and showed that these codes could be used to build a quantum computer out of slightly noisy components.

A HISTORICAL PERSPECTIVE ON QUANTUM COMPUTING

PETER WILLISTON SHOR

Member, AT&T Laboratories – Research

I am being recognized by the King Faisal International Awards in large part for my work on quantum computing. A quantum computer is a hypothetical machine which uses the principles of quantum mechanics for computation. While digital computers are based on bits, which can be either 0 or 1, quantum computers are based on quantum bits, which are two-dimensional quantum systems that can be in superpositions of states corresponding to 0 and 1; that is, quantum bits can take both values 0 and 1 at the same time. In this paper, I will try to briefly put my work on quantum computing into historical perspective.

I will open by asking a question which I suspect most of the readers can answer: What is the difference between a physics experiment and a computer? There are many possible answers to this question; one is that a physics experiment answers physical questions and a computer answers mathematical questions. Thus, if one wanted to determine the prime factors of a large number, it would seem most natural to use a computer; we will later see that it might be much more efficient to use a quantum computer, which is likely to closely resemble a physics experiment.

Another answer to the question is that a physics experiment is generally a large, custom-built device, and a computer is small box that sits on a desk. This was not always true. The first computers were huge, custom built machines which had much less computing power than is contained in current consumer devices such as CD players, cellular phones and automobiles. Computers are now commodity products, while physics experiments are still custom-built, finicky devices. What happened? This is explained by the fact that, to answer a new question about physics, one often needs to build a new and different physics experiment, whereas one basic design for computers suffices to answer any mathematical question. The economics of mass production thus apply to computers but not to physics experiments. This is a deep fact about the nature of computation, discovered by Alan Turing before the first electronic computers were built. His ideas were incorporated into real computers by John von Neumann.

Around 1936, four papers appeared that drew a distinction between computable and noncomputable functions. These papers were by Alonso Church, Stephen Kleene, Emil Post and Alan Turing; they were part of the mathematical developments following Kurt Gödel's proof of the incompleteness theorem stating that there are true mathematical propositions which cannot be proved. These four papers contained three considerably different definitions of what it meant for a function to be computable, but it was soon shown that these three definitions led to the same class of computable functions. This led to the proposal of the Church-Turing thesis, which states that this class of functions is indeed the class of functions which can be effectively computed in the real world.

After the development of real computers, it became clear that the distinction between computable and noncomputable was too coarse. What was needed was a distinction between functions which can be computed in practice and functions for which all algorithms are too time-consuming to be useful. In the 1960s and 1970s, a compromise between theory and practice was reached with the definition of polynomial-time computable functions. These are functions which can be calculated on a computer using a number of steps which grows only polynomially in the length of the input. This set of functions is called P, for polynomially-time computable. It has the property that most natural functions which are efficiently computable in practice lie in P, and conversely that most natural functions in P have algorithms fast enough to be reasonably practical.

For the class P to be independent of the type of computer used for computation, a strengthened version of the Church-Turing thesis is needed. This strengthened version has appeared under various names, and it says that the resources required by different types of computers to compute a function do not vary by more than a polynomial amount. This is not a mathematical theorem, as there is no rigorous mathematical definition of computer attached to this thesis. Instead, it is a statement about the physical world, and thus about the laws of physics. That quantum computers appear to violate this strengthened version of the Church-Turing thesis was a great surprise to many computer scientists.

To construct a counterexample to this strengthened Church- Turing thesis, one might use physical systems which are very difficult to simulate on classical computers. Two such systems are quantum mechanics and turbulence. That turbulence is still difficult to simulate is shown by the use of wind tunnels for this purpose; however, I do not know whether turbulence can be used for computation. On the other hand, it now appears that quantum computers, if they

can be built, could carry out certain interesting computations much faster than digital computers.

The first person to consider quantum computers was Paul Benioff, who asked whether quantum systems could carry out classical computation as It is performed on digital computers; he was able to resolve this question in the affirmative. Consideration of quantum computers was taken one step further by Yuri Manin in the Soviet Union in 1980, and Richard Feynman in the United States in 1982. Building on the realization that simulating quantum systems could require exponential resources on digital computers, they wondered whether computers based on quantum principles could perform better. David Deutsch, in 1985, asked the further question of whether a quantum computer could solve classical problems more quickly. Eventually, in 1992, Deutsch and Richard Josza discovered a problem that a quantum computer could solve more quickly than a digital computer. In a sequence of papers, by André Berthiamue and Gilles Brassard, by Ethan Bernstein and Umesh Vazirani, and finally by Daniel Simon, examples were discovered which successively better illustrated how quantum mechanics could speed up computation. By examining Simon's paper, I was able to show in 1994 that quantum mechanics could speed up a problem about which people cared. This problem was that of factoring large numbers into prime factors; it is important because the widely used RSA cryptosystem (named after its inventors, Ron Rivest, Adi Shamir and Len Adleman) depends on the difficulty of factorization to keep encoded data secure. This discovery energized the field of quantum computation, and it has since grown into a substantial research effort.

When my factoring paper was first announced, one widespread response was that quantum computers could never work because of decoherence and inaccuracy. Decoherence is the process whereby coherent superpositions of quantum states lose their quantumness and become one of their component states. One can calculate the severity of this problem: Suppose that a quantum algorithm requires one billion operations to perform a given calculation (approximately what is required to factor cryptographically interesting numbers). To complete the computation successfully, each step must then be performed with inaccuracy and decoherence at most one part in a billion. Achieving this accuracy requirement is possible for certain physical experiments, but is very difficult, and it appears virtually impossible for any physical system sufficiently complex to be used as the basis of a quantum computer.

Does this mean that quantum computers are destined to remain forever hypothetical machines? Not necessarily. Looking back at the early history of

classical computers, the same objection was raised in the 1950s to argue that digital computers could never perform long calculations. This objection was wrong on two counts; first, it has turned out to be possible to build computer hardware with an exceptionally small probability of failure, and second, even if this were not the case, reliable computers could be built from unreliable components with only a moderate amount of overhead. Von Neurnann realized this second point, and refuted this objection both in lectures and in a subsequent, more detailed, paper.

Can the same techniques be applied to quantum computers? At first, it was widely believed that they could not. This belief rested on fundamental properties of quantum mechanics: the Heisenberg uncertainty principle, which states that the complete state of an unknown quantum system cannot be measured, and the no-cloning theorem, which states that an unknown quantum state cannot be duplicated. I now examine four known fault-tolerance techniques, show why it appeared that fault-tolerant quantum computers could not be built, and discuss which of these classical techniques can be extended to quantum computers.

The first of these techniques is consistency checking. During a computation, there may be relationships which must hold between various intermediate results. For instance, in a calculation involving probabilities, there may be several numbers whose sum must be one. The technique would be to compute this sum, and check whether it is indeed equal to one. If it is not, an error has occurred. However, it is not clear how to correct this error except by starting the computation over from the beginning. This is the limitation of the technique; it is indeed possible to extend it to quantum computation, but unless it is used in conjunction with other techniques, it does not go very far towards making quantum computers reliable.

A second technique for fault tolerance is checkpointing. During a computation, one can periodically store the state of the computer; if the computation is found to be in error after a checkpoint, the computation can be restarted at the latest correct checkpoint rather than at the beginning. This technique cannot be extended to quantum computation, as storing the state of the computer entails making a copy of a quantum state, which is impossible.

The third technique used to make classical computers reliable is massive redundancy. Several copies are kept of all the numbers involved in the computation, and these copies are continually compared with each other to correct any errors that arise in them. This technique can be adapted to quantum computers, but it is not as powerful as it is for digital computers, and so is not

sufficient to permit arbitrarily long computations. The problem is not making copies of the input data; these can be assumed to be classical or to be known quantum states, so any number of copies can be constructed. The difficulty is rather in correcting any errors that arise. Suppose that one of several copies of an intermediate quantum state is found to be incorrect. For a digital computer, this error is corrected by duplicating one of the correct copies and using it to replace the faulty copy. The no-cloning theorem shows this to be impossible on a quantum computer, and the best alternative corrects only some of the error and spreads the rest among the various copies of this quantum state.

The final technique we consider is that of error-correcting codes. In digital computation, these are used to store data using noisy media and to transmit data over noisy channels. Error correcting codes work by computing several redundant parity check bits. These bits are arranged so that if there is an error in a block of bits in memory, not only can it be detected, but also if only a few of the bits of this block are in error, they can be corrected. At first, error correcting codes seemed impossible to extend to quantum systems, since deriving the parity check bits appeared to require copying. This intuition was incorrect; Andrew Steane and I independently discovered quantum error correcting codes. The parity check bits in these codes are not derived by copying other quantum bits, but are computed from them using operations permitted by quantum mechanics. Rather than copying the data to be encoded, quantum error correcting codes in some sense spread the data out so the quantum state is distributed over more quantum bits.

It remains to explain how the correction process in quantum error correcting codes evades the non-cloning theorem. Let us consider a specific example: a code mapping one quantum bit to five quantum bits. This code can perfectly correct any error confined to only one quantum bit. This is possible because measuring just one of the five quantum bits gives no information about the encoded quantum state, thus permitting the encoded quantum state to remain undisturbed. The encoded state can be recovered from any four correct quantum bits; one makes a measurement that identifies the error, if one exists, without measurilig the encoded state. The error can then be corrected, while the encoded state remains undisturbed.

The existence of quantum error correcting codes is not sufficient to design fault-tolerant quantum computers. For this, two extra ingredients must be developed. It must be possible to compute fault-tolerantly on encoded quantum bits, and to correct errors using noisy quantum operations, without introducing on the average more errors than are corrected. These processes both must be

performed without decoding the encoded states, since decoding would expose them to error. I developed the first techniques for doing this; they were quickly improved to show that if quantum operations can be conducted with errors and decoherence of at most one part in a million, then quantum fault tolerant computers can be developed. The latest results have reduced this error threshold to approximately one part in a thousand, giving hope that practical quantum computation might be possible without extreme precision in quantum state manipulation.

There have been numerous proposals of how to build quantum computers, using quantum bits which range from the spins of nuclei of atoms to the magnetic flux quantum states of superconductors. It is too early to tell which, if any, of these proposals will ultimately be successful, but physicists are working on many of them; in several areas the potential to build quantum computers has given a new direction to experimental investigations. To date, the largest quantum computer prototype built contains only seven quantum bits; it was able to factor only the number 15 into the product of 5 and 3. However, I am hopeful that the investigations will ultimately lead to a working quantum computer, possibly several decades away. Even if they do not, these investigations are certain to shed new light on both the theory of computation and on quantum physics.

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2002 winners meet HRH Prince Sultan ibn Abd Al-Aziz,
Second Deputy Premier, Minister of Defence and Aviation
and Inspector General
Prior to the official awards ceremony

L to **R:** Engineer Dia Al-Din Husni Mahmud Husain,
Professor Husam Al-Din Amin Al-Khatib, Professor Finn Waagstein,
HH Shaikh Dr. Sultan ibn Muhammad Al-Qasimi,
HRH Prince Sultan ibn Abd Al-Aziz, Professor Peter Williston Shor,
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