جائزة الملك فيصل العالمية
King Faisal International Prize

ARTICLES IN MEDICINE AND SCIENCE VII

THE 2007 KING FAISAL INTERNATIONAL PRIZE

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KING FAISAL
INTERNATIONAL PRIZE

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)

2007 Prize Awards in Medicine and Science

The 2007 awards were presented in April 2007

The Prize for Medicine (Topic: Prostate Cancer) has been awarded jointly to: Professor Fernand Labrie (Canada) and Professor Patrick C. Walsh (USA)

Professor Labrie is recognized for developing LHRH agonists and combined androgen blockage in the treatment of Prostatic Cancer - these innovative procedures have replaced orchiectomy (surgical removal of the testes) and estrogen therapy, and changed the quality of life of prostate cancer patients. He has also evaluated early detection procedures for prostate cancer which helped increase the patients' chances for survival.

Professor Walsh is renowned worldwide for developing nerve sparing radical surgery for prostate cancer, thereby contributing substantially to improved survival and eliminating the possibility of impotence and incontinence. He has also made important contributions towards better understanding of some genetic aspects of prostate cancer and hypertrophy.

The prize for Science (Topic: Chemistry) has been awarded jointly to: Professor James Fraser Stoddart (UK)

Professor Stoddart is a pioneer in the development of a new field in chemistry dealing with nanoscience. He is awarded the Prize for his work in molecular recognition and self-assembly. His introduction of quick and efficient template–directed synthetic routes to mechanically interlocked molecular compounds is of seminal importance. It has changed dramatically the way chemists think about molecular systems and how they can be used in the fabrication of molecular switches and machines such as molecular Elevators and shuttles.

Stoddart's work was cleverly, elegantly and meticulously done, and carries tremendous creativity, originality and innovation.

WINNER OF THE 2007
KING FAISAL INTERNATIONAL PRIZE
FOR MEDICINE

Medal: King Faisal International Prize for Medicine

Professor Fernand Labrie
Co-Winner of the 2007 King Faisal International
Prize for Medicine

Synopsis of Achievements
Professor Fernand Labrie

Professor Fernand Labrie was born in Quebec in 1937. He graduated with a BA (*magna cum laude*) from the Séminaire de Québec in 1957, received his MD (*magna cum lauda*) in 1962 and PhD. (*summa cum lauda*) in endocrinology in 1966 from Laval University. Between1966-1969, he pursued postdoctoral studies at Sussex and Cambridge universities in England, and became a Fellow of the Royal College of Physicians of Canada in 1973. He joined the faculty of Laval University in 1966 as an Assistant Professor becoming an Associate Professor in 1969 and a full Professor in 1974. He has founded the Molecular Endocrinology Research Laboratory at Laval, and has been serving since 1972 as Head of the Department of Molecular Endocrinology at the Centre Hospitalier de l'Université Laval (CHUL) and full time physician in the Department of Medicine, and from 1983 onward as the Research Director of the CHUL Research Center where about 150 senior investigators, 450 graduate students and 600 members of research personnel are currently working under his leadership. He was also Head of the Department of Physiology and Anatomy at Laval University Medical School from 1990-2002, President of the FRSQ from 1992-1995 and President of the Canadian Society of Endocrinology and Metabolism (1978-1979) and the Canadian Society for Clinical Investigation (1981-1982) and vice-President of the International Society of Neuroendocrinology (1992-1996).

Professor Labrie is one of the most accomplished scholars in the international scientific community. He has published more than 1100 scientific articles, with a total of over 40,000 citations, which makes him the most cited Canadian scientist in the world. Professor Labrie's most important contribution to prostate cancer research has been the design and clinical application of luteinizing hormone releasing hormone (LHRH) agonists for the treatment of the disease. This ground-breaking treatment strategy, generally referred to as "reversible chemical castration," has replaced the surgical removal of the testes (orchiectomy) and the use of high doses of female hormones (estrogens), which were the standard treatment methods for prostate cancer. With LHRH agonists, both the psychological disadvantage of orchiectomy and the cardiovascular complications of high estrogen doses have been eliminated and the quality of life of prostate cancer patients dramatically improved. Another medically important contribution by Labrie has been the development and clinical application of a new combined hormone

therapy[1] (combined androgen blockade) which can induce a complete cure of localized prostate cancer and extend patient's survival in metastatic cases. Professor Labrie and his group have also pioneered the screening and detection of prostate cancer. They devised the first randomized study on the use of prostate-specific antigen as a pre-screening test that could help, along with other tests, in detecting prostate cancer at an early and curable stage. In short, Professor Labrie and his team have brought a successful paradigm of prostate cancer treatment which is now helping hundreds of thousands of patients worldwide.

Professor Labrie's outstanding contributions to molecular endocrinology and oncology have been recognized by many awards and distinctions. In 1979, he was elected a Fellow of the Royal Society of Canada. In 1981 he was made an Officer of the Order of Canada, being cited as "one of the leading authorities in contemporary endocrinological research". In 1991, he was made an Officer of the National Order of Quebec and in 1999.he was awarded the prestigious Izaak Walton-Killam Memorial Prize of the Canada Council for Arts. He is also the recipient of the Medal of the College de France (1982). Professor Labrie is a member of around 69 professional associations and has been invited on more than 475 occasions to present his work at national and international symposia and Lectureships. He has also served as a member, associate member or corresponding member of the editorial boards of many leading scientific journals in his field of specialization.

Professor Labrie's rich biography not only reflects his extraordinary capabilities as a researcher, educator, administrator and physician but also gives some insight into his personal hobbies, chief among which is apparently skiing. He was the President of the Quebec Ski Federation (1982-1987) and Quebec Water Skiing Association (1987-1989) and Member of the Council of the Canadian Ski Association (1982-1987) and was Chairman of the Committee of Quebec City for the Winter Olympic Games of 2010...

LHRH agonists are now used worldwide and are regarded as probably the most efficient and best tolerated class of drugs ever discovered for the treatment of prostate cancer.

[1]A combination of either LHRH agonists with non-steroidal anti-androgens to induce blockage of androgen production from the testes and blockade of the action of the androgens of adrenal origin.

Men Should Not Die From Prostate Cancer Anymore With The Simple Application Of Today's Knowledge

Professor Fernand Labrie
Laboratory of Molecular Endocrinology and Oncology
Le Centre Hospitalier de l'Universite Laval
2705, boul. Laurier, Ste-Foy
Quebec G1V 4G2
Canada

One in eight men will be diagnosed with prostate cancer during his lifetime. Prostate cancer is a major medicosocial problem comparable to that of breast cancer in women. Despite the 33% decrease in deaths from prostate cancer in the United States during the last fifteen years between 1992 and 2007 as estimated by the American Cancer Society (Jemal *et al.*, 2007), prostate cancer remains the second cause of cancer deaths with 27 050 deaths predicted for 2007.

Discovery of medical castration with GnRH agonists

Medical castration with GnRH (gonadotropin-releasing hormone) agonists has replaced surgical castration and high dose estrogens.

GnRH is a hypothalamic hormone that controls the secretion of LH (luteinizing hormone) and follicle-stimulating hormone (FSH) by the anterior pituitary gland (Fig. 1). The elucidation of its structure was a major breakthrough (Burgus *et al.*, 1971; Matsuo *et al.*, 1971) that offered the opportunity of designing peptides much more potent than GnRH itself. Within 4 years of the determination of its structure, super-agonists of GnRH with 100–200 times its *in vivo* biological activity were already available.

When, three decades ago, we first treated experimental animals with a GnRH super-agonist, we expected to see an increase in the weight of the seminal vesicles and prostate. However, to our surprise, we observed the opposite effect: the prostate, seminal vesicles, and testicles all became smaller after a few days of treatment. Although experiments with rats suggested that GnRH agonists could have some inhibitory effect on testicular function, we discovered in 1979 at the Laval University Medical Center that complete medical castration is easily achieved in men through chronic administration of a GnRH agonist. In fact, when we administered for the first time a GnRH superagonist to a patient with

stage B prostate cancer, 70% and 85% reductions in the serum levels of testosterone and dihydrotestosterone (DHT), respectively, occurred as early as 2 weeks after the start of therapy (Fig. 2) (Labrie *et al.*, 1980). Shortly afterwards, when the effects of various doses of buserelin administered intranasally and subcutaneously were compared in detail, results showed that the subcutaneous route should be preferred (Faure *et al.*, 1982).

The demonstration that medical castration by GnRH agonists is well tolerated has rapidly led to the worldwide acceptance of this particularly well tolerated hormone therapy for prostate cancer. This development was very important for patients with localized disease who need long-term therapy and for whom treatment must be easily tolerable. While it was not acceptable for men with localized disease who have no pain or sign of their cancer to accept surgical removal of their testicles, the much better acceptability and exceptional tolerance of GnRH agonists opened the possibility of a series of clinical trials that all showed that the benefits of androgen blockade are much more important in localized or locally advanced compared to advanced disease.

Role of androgen blockade in the 33% decrease in prostate cancer deaths since 1992.

The lifesaving benefits of androgen blockade in prostate cancer have been largely underestimated. When compared with other cancer therapies, the results obtained are quite remarkable. An analysis of all clinical trial data in localized and locally advanced disease attributes part of the improving outlook in the field of prostate cancer to early detection and prompt radical prostatectomy, but mostly gives the credit to follow-up hormone therapy. "Hormonal treatment as a whole works ridiculously well" (Peto and Dalesio, 2003), as reported by Arnst (Arnst, 2003).

Although improvements in surgery and radiotherapy are likely to play a role, a study by Frank R. Lichtenberg (Statbite, 2004) using National Cancer Institute data obtained from 2.1 million cancer patients, has concluded that "cancer-fighting drugs improved survival rates, especially for cancer of the prostate, where drug innovations have been the greatest." (Mehring, 2004). This means that the drugs used for the treatment of prostate cancer, namely GnRH agonists and antiandrogens have been the most successful drugs in the field of cancer.

Despite the already well recognized positive effects of GnRH agonists and antiandrogens, the benefits of these two classes of drugs could be increased by 2- to 3-fold if their use was combined. This simply means that the GnRH agonists and anti-androgens should be used

together instead of separately. In fact, with early diagnosis and appropriate treatment, death from prostate cancer can now be avoided in almost all cases.

What is the scientific basis to combine castration with an antiandrogen?

An important advance in our understanding of the biology and endocrinology of prostate cancer and its major impact on treatment of this cancer is the observation that humans are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroids DHEA and its sulfate DHEA-S, which are converted into potent androgens in a large series of peripheral tissues, including the prostate (Fig. 1).

The local synthesis of active steroids in peripheral target tissues has been named intracrinology (Labrie, 1991; Labrie *et al.*, 2003; Labrie *et al.*, 2004). The active androgens made locally exert their action by binding to the prostatic androgen receptor without being released in significant amounts in the extracellular environment or the general circulation. Contrary to the previous belief that the testes are responsible for 90-95% of total androgen production in men (as could be inferred from the 90 – 95% decrease in serum testosterone observed after castration) (Fig. 3), it is now well demonstrated that the prostate makes the androgens testosterone and DHT locally in relatively large amounts.

The ultimate proof of the intraprostatic formation of androgens after castration can be seen in Fig. 3B that shows the intraprostatic levels of DHT, the most potent natural androgen, at 25%-50% of the value found in intact men (Labrie *et al.*, 1985; Nishiyama *et al.*, 2004). In fact, the prostate makes its own androgens at a level comparable to the androgens of testicular origin.

Monotherapy (GnRH agonist alone, orchiectomy alone or antiandrogen alone) is scientifically an insufficient and non recommended treatment.

Since prostate cancer is the most sensitive of all cancers to hormone therapy, any kind of blockade of androgens exerts detectable effects. However, we should not be satisfied or lured by any kind of positive result obtained with monotherapy, since they are only a fraction of what can be achieved. In fact, although significant positive results are observed with monotherapy, much better results and even cure of the

cancer can be achieved by combined androgen blockade applied to localized disease.

Monotherapy in localized disease: positive but far from optimal results are obtained.

All clinical trials of androgen blockade have shown prolongation of life or a reduced death rate from prostate cancer in patients with localized or locally advanced disease (Table 1). During 3.7-9.3 years of follow-up, these six studies have shown reductions in deaths from prostate cancer ranging from 37.5% to 81% (Bolla et al., 1997; Pilepich et al., 1997; Granfors et al., 1998; Labrie et al., 1999; Messing et al., 1999; Hanks et al., 2000; D'Amico et al., 2004). A seventh study provided no data on cancer-specific deaths, but a 45% decrease in deaths overall was reported (D'Amico et al., 2004).

Following the recent meta-analysis of androgen blockade with monotherapy in localized prostate cancer, Peto stated that "prostate cancer is usually treated with surgery or radiation, but a few cancer cells may remain and cause an often-fatal recurrence. Since the mid-80s, oncologists have increasingly followed up with either surgical removal of the testes, or with newer anti-hormone drugs "(Peto and Dalesio, 2003). The meta-analysis which looked at several studies involving 5,000 men showed that 74% of patients who received early hormone monotherapy were still alive 10 years later, compared with 62% of those who did not (Arnst, 2003; Peto and Dalesio, 2003).

It was concluded from this metaanalysis on the effect of monotherapy in localized and locally advanced prostate cancer that the risk of dying from prostate cancer within 10 years decreased by one-third if hormonal treatment was given immediately rather than after the disease had progressed (Peto and Dalesio, 2003). This one-third decrease in the risk of dying from prostate cancer was not the result of a comparison between androgen blockade and placebo (or no androgen blockade), but between early and late androgen blockade. It is also very important to consider that these results were obtained with only partial blockade of androgens or monotherapy. These data led Peto to the conclusion that "Hormone treatment as a whole works much better than previously thought".

The simple addition of a pure antiandrogen to castration (combined androgen blockade, CAB) can achieve cure in more than 90% of localized prostate cancers instead of the 33% decrease in deaths by monotherapy.

Consequently, with today's knowledge, monotherapy (castration alone or antiandrogen alone) is not an acceptable androgen blockade.

As mentioned above, GnRH agonist monotherapy in localized prostate cancer has produced important benefits in terms of survival in localized prostate cancer. However, with the knowledge that 25%-50% (Fig. 3) of androgens remain in the prostate after castration, it is logical to expect superior results from the use of CAB or the combination of an GnRH agonist with a pure antiandrogen (Table 2). Published data already indicated that the benefit is greater for patients with minimal metastatic disease than for those with extensive metastatic disease (Crawford et al., 1989; Denis et al., 1998). Evidence indicates that CAB can achieve long-term control or cure of prostate cancer in at least 90% of patients with localized or locally advanced disease (Fig. 4) provided that treatment is given continuously, uninterrupted, for at least 6 years (Labrie et al., 2002) (Table 2).

A series of recent studies performed in Japan clearly illustrate the very high efficacy of CAB in localized disease (Egawa et al., 2004; Homma et al., 2004; Akaza, 2006; Ueno et al., 2006). In a prospective study performed in stage C and D prostate cancer patients, (Akaza et al., 2004; Akaza, 2006) comparing GnRH agonist monotherapy and CAB (GnRH agonist + bicalutamide 80 mg/day), the effect of CAB was more pronounced in patients with C than with D disease. In fact, only 5.8% (3/52) progressed under CAB compared to 42.6% (20/47 events), thus showing a marked superiority of CAB compared to monotherapy, especially in stage C or locally advanced disease. These data clearly indicate that a greater effect of CAB is found in stage C compared to stage D disease. It also supports our results showing an even much greater advantage of CAB in stage B disease (Labrie et al., 2002). At least for older men, primary hormone therapy is a valid therapeutic option for localized or locally advanced prostate cancer (Akaza et al., 2006). A similar conclusion was reached in a retrospective study of 447 stage B prostate cancer patients who received androgen blockade alone or radical prostatectomy combined with androgen blockade in 86% of cases. No difference in disease-specific survival was found at 9.2 years (Egawa et al., 2004).

No resistance or loss or lack of response to combined androgen blockade exists for the treatment of localized disease.

The recognition of the absence of development of resistance to androgen blockade in localized prostate cancer is extremely important. In

fact, it is very frequently believed that androgen blockade should not be administered early because resistance to treatment will develop and one might as well wait to use androgen blockade at a later stage of the disease. In fact, deferring treatment is a very serious mistake since it implies that, very often, it will then be too late. In fact, when the cancer has reached the bones, the resistance to treatment can no more be avoided and cure is impossible. It should be realized that when prostate cancer is first detected, even by screening, the cancer is not small since its diameter is of the order of 1 cm or more. This is the only appropriate time to start treatment with the very strong hope of a cure.

Hormone therapy is not only misused but it is also greatly underused in prostate cancer.

Despite the fact that it is well recognized since the 1940s that the standard and even the only efficient treatment of metastatic prostate cancer is androgen blockade , a recent survey of 9,110 men 65 years or older who died from prostate cancer between 1991 and 2000, has surprisingly found that 38% of black and 25% of white men in the USA did not receive hormone therapy before dying from prostate cancer (Lu-Yao *et al.*, 2006). If patients with metastatic prostate cancer do not receive hormone therapy, how can we implement combined androgen blockade versus monotherapy?! (Table 3). This deficient use of androgen blockade in prostate cancer can be contrasted with the respective 93.5% and 98% rates of use of beta blockers after myocardial infarction (The State of Health Care Quality, 2003, Washington D.C. National Committee for Quality Assurance, p. 60) and tamoxifen in estrogen receptor positive breast cancer (Buzdar and Macahilig, 2005).

With today's knowledge, monotherapy is not an acceptable androgen blockade. Combined androgen blockade is more and more frequently used as first line treatment.

This deficiency in the field of prostate cancer may be due to the fact that doctors underestimate the risks of death from prostate cancer compared to other causes of death. Such data illustrate the challenge facing the application or translation of results of clinical research into clinical practice (Lenfant, 2003), especially for prostate cancer (Table 2).

Data on the current treatment of prostate cancer in Japan shows that primary androgen blockade is the treatment chosen for localized and locally advanced prostate cancer in a high proportion of cases. In the survey of the Japanese Urological Association published in 2005, androgen blockade alone was used as primary treatment in 40% of T1

patients and over 50% of T2 patients. Moreover, from the data collected in 2001, 2002 and 2003 by the Japanese Prostate Cancer Surveillance Group (J-CaP) (Akaza *et al.*, 2004), about 60% of patients who receive androgen blockade receive CAB. In addition, about 70% of patients who receive androgen blockade receive hormone therapy as first treatment. A similar trend is seen in the US from the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) (Cooperberg *et al.*, 2003).

Early diagnosis is a must in order to be able to apply a curative treatment of prostate cancer.

With the presently available techniques, screening can diagnose prostate cancer at a clinically localized stage in 99% of cases (Labrie *et al.*, 1996). Such an early diagnosis permits immediate treatment with a curative intent, combined androgen blockade (CAB) being a truly efficient alternative, especially in older patients. Most importantly, CAB must be used immediately in patients who fail radical prostatectomy, radiotherapy or brachytherapy. Moreover, when androgen blockade is used, it should always be combined androgen blockade. Using this strategy, based upon today's available diagnostic and therapeutic approaches, death from prostate cancer can be an exception, confirming that victory against prostate cancer is practically achieved.

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Table 1

Effect of the use of androgen blockade on prostate cancer death rates

Study	Advantage	Median follow-up (years)	*P*
EORTC 415 patients	77% decrease in cancer-specific death	3.7	0.01
RTOG 85-31 276 patients	37.5% decrease in cancer-specific death for Gleason score 8–10	4.5	0.03
Laval University Screening Trial 21,400 subjects	67% decrease in cancer-specific death	8	0.0002
Messing *et al.* 98 patients	81% decrease in cancer-specific death	7.1	0.001
Granfors *et al.* 91 patients	39% decrease in cancer-specific death	9.3	0.06
RTOG 92-02 1,554 patients	59% decrease in cancer-specific death for Gleason score 8–10	5	0.007
D'Amico *et al.* 201 patients	45% decrease in overall death	4.5	0.04

Table 2

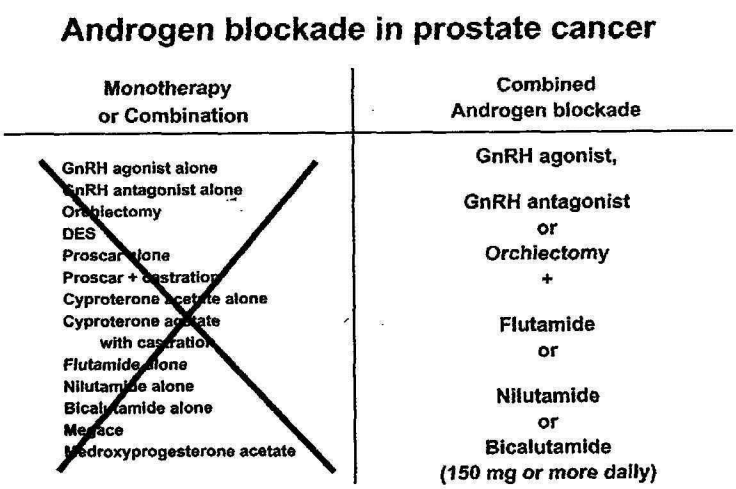


Table 3

Frequent errors related to androgen blockade

1- **Monotherapy (GnRH agonist alone, orchiectomy alone or antiandrogen alone) instead of combined androgen blockade**
2- **Too short duration of treatment**
3- **Treatment started too late**
4- **Intermittent treatment**

Legends to figures :

Figure 1. Schematic illustration of the two sources which provide androgens to the normal prostate and prostate cancer:
1) The testicles secreting testosterone and
2) The adrenals providing dehydroepiandrosterone (DHEA) which is converted into testosterone and then into DHT (dihydrotestosterone) in the prostate.

Figure 2. Effect of twice-daily intranasal administration of the LHRH agonist buserelin on serum levels of (a) testosterone and (b) dihydrotestosterone in a patient with stage B prostate cancer (Labrie et al. 1980).

Figure 3. Effect of castration + flutamide on the intraprostatic DHT levels

Figure 4. Effect of duration of treatment of localized prostate cancer with continuous combined androgen blockade (CAB) on the probability of long-term control or "cure of the disease" illustrated by no rise of prostate-specific antigen (PSA) for at least 5 years after cessation of CAB. The point at 4.75 years of treatment (33%) refers to the 3 patients treated with CAB for 3.5-5.0 years and followed for at least 5

years, whereas the point at 5.75 years refers to the 8 patients treated continuously with CAB for 5.0 – 6.5 years before cessation of treatment. The point at 8.25 years refers to the 8 patients treated continuously with CAB for 6.5 – 9.0 years, whereas the point at 11 years refers to the 13 patients treated for 10 -11.7 years with continuous CAB before stopping treatment. All patients were followed for at least 5 years after cessation of continuous CAB or until PSA rise. Only 1 patient has died from prostate cancer, whereas 18 have died from other causes (Labrie et al., 2002).

Figure 1

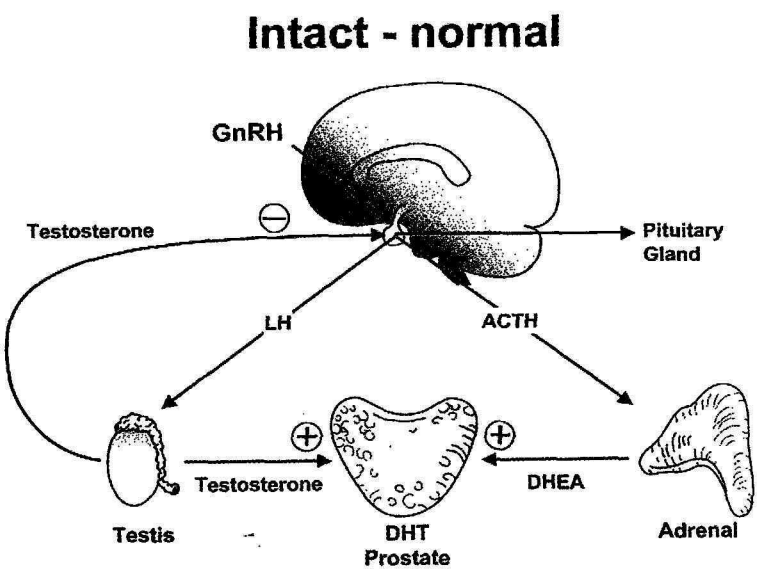
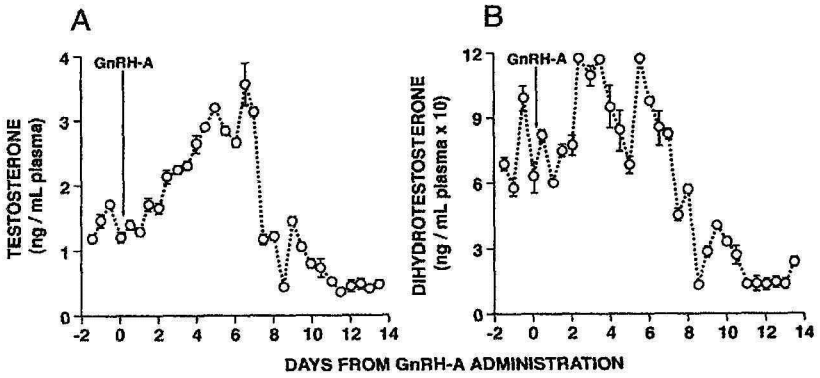


Figure 2



Effect of twice-daily intranasal administration of the LHRH agonist buserelin on serum levels of (a) testosterone and (b) dihydrotestosterone in a patient with stage B prostate cancer. (From Labrie *et al.* 1980)

Figure 3

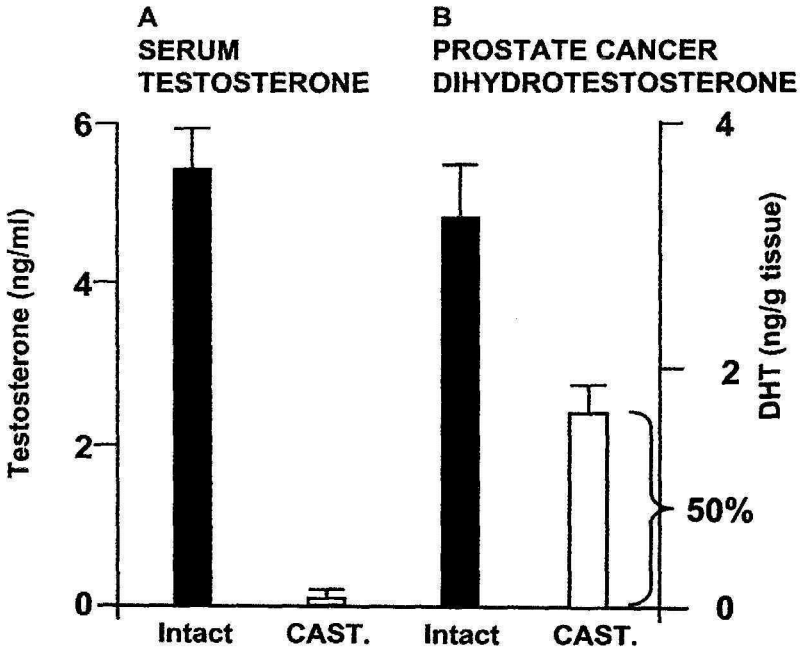
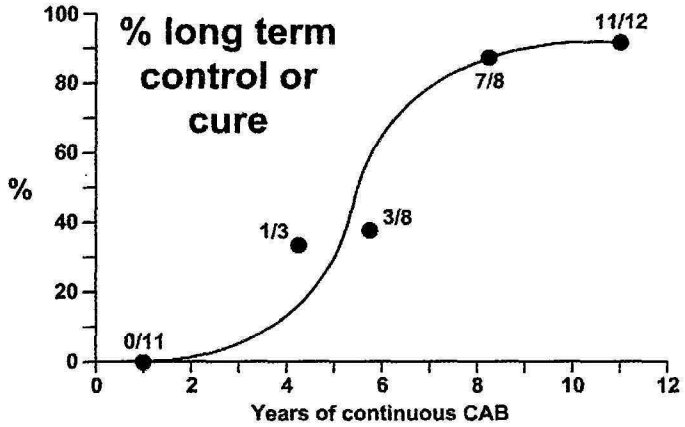


Figure 4

Effect of duration of continuous CAB on the % of patients with PSA remaining under control for a minimum of 5 years following cessation of CAB



Labrie et al, Urology 60;115-119, 2002

Professor Patrick C. Walsh
Co-Winner of the 2007 King Faisal International Prize for Medicine

Synopsis of Achievements
Professor Patrick C. Walsh

Professor Patrick Craig Walsh (b. 1938) was the David Hall McConnell Professor and Director of Urology at the James Buchanan Brady Urological Institute of the Johns Hopkins University Medical School in Baltimore, MD for thirty years (1974-2004). Under his leadership, he developed one of the most outstanding urology departments in the world. In 2004 he stepped down from his administrative responsibilities to devote more time to research writing and his patients. He is presently Distinguished Service Professor of Urology at Johns Hopkins Medical School and Hospital.

Professor Walsh received his bachelor's (1960) and MD (1964) degrees from Case Western Reserve University in Ohio, followed by an internship and residencies in adult and pediatric surgery at the Peter Bent Brigham Hospital and the Children's Hospital Medical Center, respectively, in Boston, MA. He then took up a residency in Urology and fellowship in endocrinology (1967-1971) at the University of California in Los Angles (UCLA); and was certified in 1975 by the American Board of Urology. After completing his residency in UCLA, he spent two years of military service at the Naval Hospital in San Diego, CA, then joined the laboratory of Professor Jean Wilson at the University of Texas Southwestern Medical School in Dallas for one year. Together with Wilson, they published the first description of the 5a-reductase enzyme deficiency, and were the first to develop a technique for the induction of benign prostatic hyperplasia (BPH) using dogs and to demonstrate the effect of reversible androgen deprivation on BPH. From 1974, he took the position of professor and director of urology at the James Buchanan Brady Urological Institute at Johns Hopkins.

Professor Walsh is recognized worldwide as the inventor of nerve sparing radical prostatectomy (complete surgical removal of the prostate gland) for the treatment of prostate cancer; which substantially improved the potency and continence of prostate cancer patients and enhanced their quality of life. His technique, which also reduces significantly the risks of post-operative mortality and progression to metastasis, has become one of the most widely used strategies for the treatment of organ confined prostate cancer. A strong proponent of prostate cancer surgery and the leader in this field, he produced a detailed description of his surgical technique in a DVD that was distributed free of charge to 50,000 urologists worldwide. He has also made significant contributions towards

better understanding of hereditary aspects, pathogenesis and susceptibility genes of prostate cancer. In addition, he demonstrated the value of serial prostate specific antigen measurement as a means for improving the diagnosis of prostate cancer and developed nomographs for predicting the outcome of the illness. .

Professor Walsh has authored or co-authored more than 430 papers, 3 books and 8 motion pictures and is the second most cited author in the field of prostate cancer according to ISI. His achievements have been recognized by more than 20 academic awards and honors, including the Grand Officer of the Order of Leopold, presented by the Belgian Monarch, and, in recent years, by the Charles F. Kettering Medal from the General Motors Cancer Research Foundation, the American Academy of Achievements Golden Plate Award, The American Urological Association Distinguished Service Award and Sir Peter Freyer Memorial Medal from the University College, Galway, Ireland. He is a member or honorary member of many professional associations and societies including the Institute of Medicine of the National Academy of Sciences and is the President of the American Association of Genitourinary Surgeons. In 2004, he was elected an Honorary Fellow of the Royal College of Surgeons of Ireland and an Honorary Fellow of the Royal College of Surgeons of England. A group of his former patients raised $25 million to support research of outstanding scientists at Johns Hopkins. The fund was named The Patrick C. Walsh Prostate Cancer Research Fund in his honor

Professor Walsh has served as a visiting professor or guest lecturer nationwide and worldwide. Among his named lectures are: the David D. Day Lecture, the Bruce Stewart Lecture, the Southern Lecture and the Ramon Guiteras Lecture. He has also been a consultant to the U.S. Naval Hospital, Walter Reed Hospital, the Clinical Centers and the National Cancer Institute of the National Institutes of Health, the Advisory Board of the National Institute of Diabetes, Digestive and Kidney Diseases, the Food and Drug Administration and several local hospitals in the Baltimore area. Furthermore, he has served on the editorial boards of several medical journals of urology and surgery and is presently a member of the editorial board of the New England Journal of Medicine. He served as the Chief Editor of the renowned Campbell's Textbook of Urology for 25 years and in recognition of his contributions, the 4-volume, 4000 page textbook has been named Campbell-Walsh Urology. Along with Janet F., Worthington he authored two of the best selling books on prostate cancer for general readers, namely: "The Prostate: A Guide for Men and the Women Who Love Them" published in 1995 and

1997, and "Dr. Patrick Walsh's Guide for Surviving Prostate Cancer" published in 2001.

His hobbies include swimming and cycling.

> *"[Professor Patrick's] work on the surgical anatomy of the prostate and the technique of radical prostatectomy have an every day impact on virtually every urologist and urologic surgeon in the world."*

The Discovery of the Nerves Responsible for Erectile Function and Development of Nerve Sparing Radical Retropubic Prostatectomy

Patrick Craig Walsh, M.D.
James Buchanan Brady Urological Institute
The Johns Hopkins Medical Institutions
Baltimore, MD 21287-2101
USA

April 26, 2007 marks the twenty-fifth anniversary of the first purposeful nerve sparing radical retropubic prostatectomy. At that time, 1982, virtually all men who underwent surgical treatment for prostate cancer were impotent postoperatively. However, in contrast this patient had complete recovery of sexual function within nine months following surgery and twenty-five years later has retained his quality of life and an undetectable PSA. This account of the events that led up to that operation illustrates the influence of serendipity on discovery.

BACKGROUND

Radical perineal prostatectomy was first developed at the Johns Hopkins Hospital in 1904 by Hugh Hampton Young and in 1947 the retropubic approach was introduced by Terence Millin.[1, 2] Although radical prostatectomy provided excellent cancer control it never gained wide-spread popularity because of major side effects. Virtually all men who underwent surgery were impotent, many had significant urinary incontinence, and when performed via the retropubic approach excessive bleeding was common. With the introduction of external beam radiotherapy for the treatment of prostate cancer, it was possible to avoid many side effects. Thus, by 1970, radical prostatectomies were rarely performed because it was perceived that the side effects of the treatment were worse than the disease.

In 1974, shortly after I arrived as the new director of the Brady Urological Institute, I embarked upon a series of anatomic studies in an attempt to understand the source of the side effects from

radical prostatectomy with the hope that they might be avoided. Soon it became clear that excessive bleeding occurred because the anatomy of the venous complex was not charted, impotence was universal because the location of the nerves to the pelvic organs and the erectile bodies in the penis were not known, and incontinence was common because the anatomic understanding of the sphincteric complex was incorrect. This deficit in the understanding of the anatomy surrounding the prostate can be traced to the use of adult cadavers, which were not ideal for these investigations. The agents used for tissue fixation dissolve adipose tissue, thus obscuring normal tissue planes, and the abdominal organs compress the pelvic organs into a thick pancake of tissue making anatomic dissection difficult. These problems were overcome by using the operating room as an anatomy laboratory and through the use of infant cadavers for anatomic study.

THE DISCOVERY

I had the opportunity to train at excellent centers on both the East and West coasts of the United States where experienced pelvic surgeons would encounter tremendous blood loss when dividing the veins surrounding the prostate without ever commenting on why it occurred or how it might be avoided. For this reason I first embarked upon defining the anatomy of the venous complex, which is obscured by the dense overlying fascia. In the operating room it soon became clear that there was a common trunk overlying the prostate where it could be divided safely.[3] In February 1977, shortly after I had worked out the technique for controlling bleeding from the dorsal vein, a 58-year-old patient from Philadelphia told me that he was fully potent within a year following his radical prostatectomy. From this one observation, I knew that the belief commonly held by urologists that the nerves ran through the prostate was incorrect. That same year I attended my first meeting of the American Association of Genitourinary Surgeons (AAUGS). The night before the meeting my wife and I went to a restaurant and there, standing in the shadows behind the maitre'd, I spotted an older man. Impetuously, I asked if he was also attending the same meeting and whether he would like to join me and my wife for dinner. That night was the first time I met

Pieter Donker, the Professor and Chairman of Urology at the University of Leiden. At dinner I learned a lot about his career and he about the training program at Hopkins. As a result the following year one of his residents, Jaab Zwartendijk, joined us for a one year fellowship further cementing my relationship with Donker.

For the next several years I took every opportunity I could to learn more about the anatomy of the pelvic nerves and the location of the branches responsible for erectile function. Unfortunately, the anatomy texts in that era were not very helpful and contained no information on the exact anatomical location of the nerves to the erectile tissue. Long after the discovery was made, however, two articles published many years earlier were called to my attention that did provide some of this information. [4, 5]

In February 1981 I was invited to attend a meeting in Leiden, the Netherlands. Although I had expected to do some sightseeing, it didn't work out that way. Instead, I ended up spending a week in operating rooms, laboratories, and lecturing. On the final day before we returned to the United States, Friday, February 13, 1981, my 43rd birthday, my host offered a tour of Leiden and because of my previous friendship with Pieter Donker he asked Pieter to be my guide. Had it not been for that dinner four years earlier we would have never met and this opportunity would have been missed.

Pieter offered to show me the windmill museums, the canals, and other local sights. However, I was interested in what he was doing now that he had retired and when he told me that he was working in the anatomy laboratory I told him that I would like to see what he was doing, without any idea of the connection between his work and my interest. We went to the beautiful anatomy building at the University of Leiden that has a museum. In the basement of the anatomy building Pieter took out an infant cadaver, a dissecting microscope, and his drawings. When I asked why he was dissecting out the nerves to the bladder, he stated that this had never been done successfully before and when I asked why he was using the infant cadaver, he stated that this was the best model,

avoiding the complications described above with the use of adult cadavers. When I looked at his drawings I asked about the location of the branches to the erectile tissue. He stated that he had never looked. Three hours later both of us could see that the nerves were located outside the capsule and fascia of the prostate. Figure 1. is my illustration from that day showing how important discoveries can have humble beginnings.

Over the next year Pieter continued to perform dissections and I once again used the operating room as an anatomy laboratory. Based upon the findings in the infant cadaver we had a schematic diagram of where the nerves were located, but no landmarks to identify their location in the adult male pelvis.[6] Over the next year I noticed that there was a cluster of vessels, the capsular arteries and veins of the prostate, that traveled in this exact location. In March 1982 I met once again with Pieter at the AAGUS meeting and he agreed with my suggestion that these vessels provided the scaffolding for the nerves and that the neurovascular bundle could be used as the macroscopic landmark to identify them during surgery.[7]

I returned to Baltimore and in March 1982 performed a radical cystectomy for bladder cancer, in which the prostate and bladder are removed, on a 60-year- old man. I'd never seen a patient who was potent following a radical cystectomy, but ten days postoperatively the patient awoke with a normal erection. On April 26, 1982 I performed the first purposeful nerve sparing radical prostatectomy on a 52-year-old professor of psychology from Cleveland, Ohio and within seven months he was fully potent. Today he is cancer free with an excellent quality of life. The final two pieces of the puzzle came together shortly thereafter. Although everyone who performed prostatectomies was familiar with the tissue that covers the rectal surface of the prostate, little or nothing had been written about the layers of tissue on the sides of the prostate. However, based upon a whole mount step sectioned prostate that was harvested by Herb Lepor when he was a resident, it became clear that these layers were divided into two layers – the prostatic fascia and the levator fascia and that when nerve sparing is properly performed the prostatic fascia must remain on the

prostate.[7] Subsequently, Herb Lepor and Peter Schlegel provided documentation of the precise location of the cavernous nerves. [8, 9] The role of Leon Schlossberg, the noted medical illustrator, in translating these discoveries into anatomically accurate drawings cannot be overstated. His knowledge of anatomy and his ability to translate what he saw in the operating room to paper made it possible to share these discoveries with surgeons around the world.

Development of the technique for ligation of the dorsal vein not only reduced blood loss, but was also associated with improvement in urinary control. The reason for this became evident from a review of Olerich's 1980 publication which demonstrated that the sphincteric complex responsible for passive urinary control was a vertically oriented tubular sheath that embraced the apex of the prostate.[10] This anatomy had important implications in transection of the dorsal vein complex, which is intimately associated with the striated sphincter. Before the anatomic approach was developed, surgeons cut through the dorsal vein complex immediately adjacent to the pelvic floor. In these cases the dorsal vein retracted out of sight and could not be controlled and the anterior major portion of the striated sphincter was excised. However, with improved approaches to control of hemostasis more of the anterior striated sphincter was preserved, thus resulting in improved urinary control.

THE IMPACT

This discovery came at a critical time in the field of urology. When I finished my training in the early 1970s, the most common open surgical procedures performed by a urologist were pyelolithotomy, ureterolithotomy, open simple prostatectomy, simple nephrectomy, and exploration for a renal mass. With the development of improved imaging, renal exploration was performed less frequently. Then in the early 1980s, with the advent of extra corporeal shock wave lithotripsy and percutaneous renal surgery, much of the open surgery performed by urologists was eliminated. Because of side effects radical prostatectomies were rarely performed. Indeed in 1980, nationwide only 7% of men with localized prostate cancer underwent surgery. However,

armed with the ability to cure prostate cancer with surgery with fewer side effects, radical prostatectomy was rapidly adopted, not only because it was possible to preserve potency, but also because the operation became safer once the anatomy of the dorsal vein complex was understood. Over the years the 30 day mortality of radical prostatectomy has fallen ten-fold, from 2% to 0.2%. By the mid 1990s, 35% of men with localized prostate cancer underwent surgery nationwide. Had this operation not come along, the scalpel would have been literally removed from the hands of many urologists and who knows what would have happened when PSA made it possible to identify so many men with curable disease?

The improved popularity of radical prostatectomy may also be responsible for the dramatic decrease in prostate cancer deaths over the last decade. Based on the findings from the Scandinavian Prostate Cancer Group's randomized trial of radical prostatectomy versus watchful waiting, at ten years there was a 44% reduction in death from cancer (15% in the watchful waiting group versus 10% in the radical prostatectomy group). Recognizing that in 1992 104,000 men underwent a radical prostatectomy in the United States, if surgery reduced prostate cancer deaths by 5% ten years later, this could have reduced deaths from prostate cancer in the United States by 5,000, explaining much of the observed decline (35,000 versus 27,000).

However, one could argue that the most important impact has been on the field of research in prostate cancer. Up until the early 1980s we knew very little about prostate cancer and had difficulty improving our knowledge. There was little tissue for scientific investigation other than small needle biopsy specimens. Most men were treated with external beam radiotherapy and thus it was impossible to know the true extent of disease at diagnosis and to know whether or not their disease had been controlled. Instead, we had to wait for fifteen years to see whether the patient died from prostate cancer. However, once radical prostatectomy became more widely available we were able to know for certain the pathologic stage of disease and were able to use this as a surrogate for predicting the probability of cure. Once PSA became available, we were able to use these data to establish the Partin Tables to

predict the probability of cure. Further more, with the availability of tissue it was possible to carry out biochemical and genetic studies into the molecular pathogenesis of the disease which heretofore were impossible.

I share these thoughts not to take major credit, but to describe how important discoveries can be made – a simple act of kindness to a lonely older man followed four years later by trying to understand what he was doing now that he was retired. Never underestimate what you can learn from others – it puzzles me why it took so long for someone to solve this problem and who knows how much longer would it have taken without these serendipitous events.

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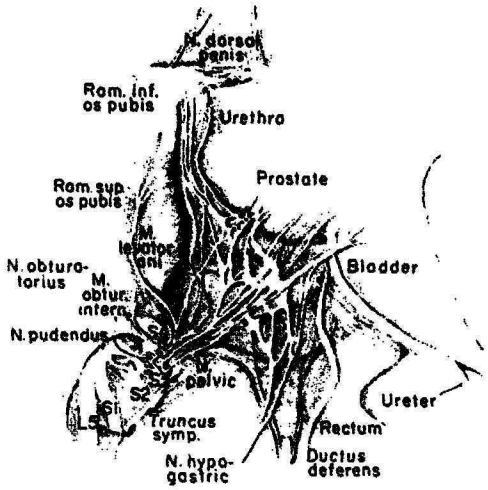
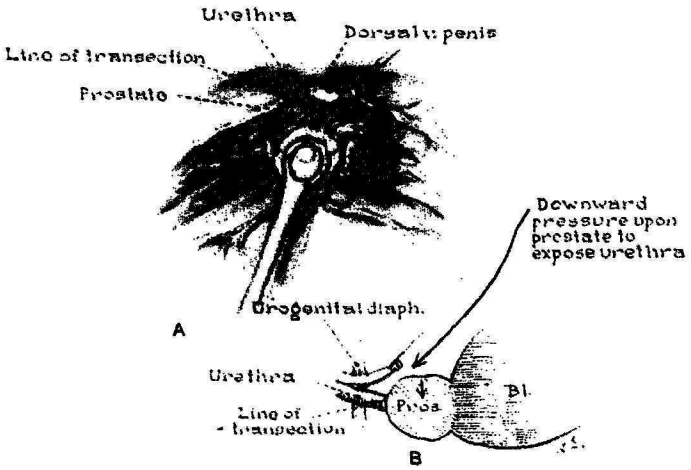
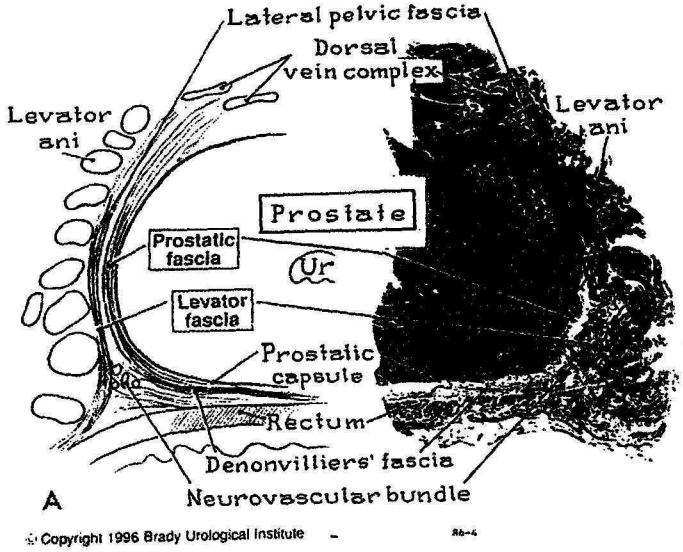
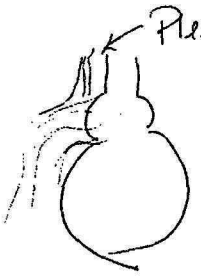

N. dorsal penis
Rom. inf. os pubis
Urethra
Prostate
Rom. sup. os pubis
M. levator ani
N. obturatorius
M. obtur. intern.
Bladder
N. pudendus
N. pelvic
S2
Gl
L5
Truncus symp.
Ureter
Rectum
N. hypogastric
Ductus deferens

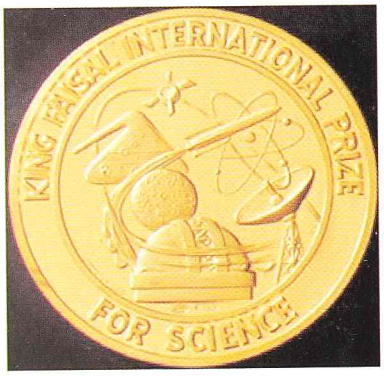

Urethra
Dorsal v. penis
Line of transection
Prostate
Downward pressure upon prostate to expose urethra
Urogenital diaph.
A
Urethra
Line of transection
Prost.
Bl.
B



Dunker - Leiden Feb 13 1981



WINNERS OF THE 2007
KING FAISAL INTERNATIONAL PRIZE
FOR SCIENCE



Medal: King Faisal International Prize for Science

Professor James Fraser Stoddart
Winner of the 2007 King Faisal International Prize for Science

Synopsis of Achievements
Professor James Fraser Stoddart

Professor Sir Fraser Stoddart was born in 1942 in Edinburgh, Scotland, and received his bachelor's and Ph.D. degrees from Edinburgh University in 1964 and 1966, respectively. In 1967, he traveled to Queen's University in Canada as a Post-Doctoral Fellow and in 1970 became an Imperial Chemical Industries (ICI) Research Fellow at Sheffield University, joining its faculty as a Lecturer the following year. Between 1978-1981, he was a Visiting Scientist at the ICI Corporate Laboratory in Runcorn and while there was awarded a D.Sc. degree by Edinburgh University for his research in stereochemistry (1980). In 1981, he returned to Sheffield University and became Reader the following year. In 1990 he joined Birmingham University as Professor of Organic Chemistry and was Head of its School of Chemistry from 1993 to1997. He then took up the Saul Winstein Professorship in Chemistry at UCLA and in 2002 became the Acting Co-Director of California NanoSystems Institute (CNSI). From 2003, he became the Fred Kavli Professor of NanoSystems Sciences and Director of the CNSI.

A world authority in mechanical chemistry and nanoscience, Professor Stoddart has created a new and promising field of chemistry by introducing mechanical bonds into chemical compounds. Using molecular recognition and self-assembly processes he is able to build mechanically interlocked molecules that can be used as functioning devices after the same style as those found in the living world. These extremely tiny nano-mechanical devices[2] operate based on the relative movements of molecular components and can be activated chemically, electrically and optically. As such, they hold considerable promise for fabrication and use as switches, sensors, actuators, amplifiers, motors, artificial molecular muscles, molecular random access memories, etc. Smaller than a human cell, some of them may also have the potential of being used to deliver drugs into cancer cells.

Professor Stoddart currently leads a large body of researchers and visiting scientists working at the interfaces of physics, materials science and life sciences with chemistry. During the past 35 years, he has trained more than 280 Ph.D. students and post-doctoral scholars, many of whom are now pursuing successful academic careers of their own. He has published more than 770 papers and delivered more than 700 invited lectures worldwide and is ranked by the Institute for Scientific Information (since 1996) as the third most-cited chemist in the world.

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[2] 1 nanometer = 1 billionth of a meter.

Stoddart's outstanding achievements in chemistry and molecular nanotechnology have been recognized worldwide by numerous awards, honorary degrees, named lectureships and visiting professorships throughout the U.S.A., Canada, Western Europe, Australia, Japan, the former USSR, China and Brazil. Among his many prestigious prizes are the America Chemical Society's Cope Scholar Award and the Nogoya Gold Medal in Organic Chemistry. He is a Fellow of the Royal Society of London, the Science Division of the Netherlands Academy of Arts and Sciences, the German Academy of Natural Sciences, the Royal Society of Chemistry and the American Association for the Advancement of Sciences. He is also a member of the editorial boards of several journals including the Journal of Organic Chemistry, Angewandte Chemie and Chemistry, and is a co-editor (with Fritz VÖgtle) of the book "Stimulating Concepts in Chemistry." In 2005, he was appointed an Honorary Professor at East China University for Science and Technology in Shanghai and a Carnegie Centenary Professor at the Universities of Scotland, and was selected the University of Edinburgh Alumnus of the Year. In 2006, he was awarded an honorary doctorate by Twente University in The Netherlands and at the turn of this year, he was named Knight Bachelor by Queen Elizabeth II of Britain.

"My work reflects the hurly-burly life of a scientific nomad through thick and thin from the Athens of the North to the City of the Angels, with brief and no so brief interludes on the edge of the Canadian Shield in the Socialist Republic of South Yorkshire, on the planes of Cheshire beside the Wirral, and in the Midlands in the heartland of Albion"

J. Fraser Stoddart

The Chemistry of the Mechanical Bond

J. Fraser Stoddart
California NanoSystems Institute
Department of Chemistry & Biochemistry
University of California, Los Angeles
405 Hilgard Avenue, Los Angeles, CA 90095
USA

This story is about my long-time association with a contemporary class of chemical bonding which is, by now, all pervasive at the molecular level of structure, not to mention being an integral part of many extended structural arrays – although I will be confining my remarks to molecules only in this discussion. The chemical bond I am alluding to is not a classical one belonging to the covalent, coordinative, or noncovalent categories – or even an electrostatic bond – but rather it is a mechanical one in which two or more molecular components become interlocked, one with another, and so on, in some manner or other.[1] Of course, some or all of the classical bonds are present in the mechanically interlocked molecular compounds I am going to mention in this article. Indeed, the presence of geometrically precise coordinative bonds and well-marshaled noncovalent bonds are fundamental and key to the introduction of mechanical bonds by templation into molecules with any kind of proficiency and efficiency. As with all stories in science, this one is about (1) discovery and invention, (2) just a glimmer of hope that there will be tangible applications one day, and (3) the talented souls who brought everything about in the laboratory and beyond in the first place.

For the most part, chemistry is about making, measuring, and modeling. Although all three of these pursuits most desirably should happen in harmony in a modern chemical laboratory, there is no doubt in my own mind that making, in the widest sense, is right at the heart of chemistry. More than a millennium ago, Jabir Ibn Hayyan was a prominent Arab alchemist who has often been referred to as "the father of chemistry," and is widely credited with the introduction of the experimental method into alchemy, as well as with the invention of numerous important processes that are still used in chemistry today. "The first essential in chemistry," he is purported to have said, "is that you should perform practical work and conduct experiments, for he who performs not practical work nor makes experiments will never attain the least degree of mastery." Indeed, it is the act of designing and synthesizing a product or a material with a particular form and/or function that distinguishes

chemistry from its cognate sciences. It was Marcellin Berthelot (1827-1907) who, in 1860, stated, "La Chimie crée son objet." – "Chemistry creates its object." He continued, "Cette faculté créatrice, semblable à celle de l'art lui-même, la distingue essentiellement des sciences naturelles et historiques." – "This creative capability, resembling that of art itself, distinguishes it essentially from the natural and historical sciences." As one of Berthelot's most fervent disciples these past 35 years, I have cajoled myself into becoming better and better each year in the art of fashioning compounds and complexes at that ultimate of size levels, the one which equates with being a chemist – namely, at the molecular level and beyond at the supramolecular one. Together with the brilliant young men and women who have gravitated towards my research group for a finite period of time, we have faced, as a team, formidable challenges, yet derived no end of pleasure from designing and synthesizing molecular compounds of a somewhat exotic nature. These exotic compounds have contained, in addition to the classical chemical bonds, a mechanical bond.

While the temptation to tell a story in chronological order is always present, let me break with this tradition and stress the importance of making in chemistry by relating how we finally succeeded,[2] after more than a decade of tussling with a challenging problem related to the Borromean Rings (BRs) – an object of particular topological interest to those versed in knot theory – in synthesizing[3] the molecular embodiment of the BRs. It is found in low dimensional topology and is comprised of three interlocked rings wherein the cleaving of any one ring results in the whole caboodle falling apart to give the ruptured ring and the two other rings which can then separate freely from one another in spontaneous fashion.

We first of all tried to tackle the synthesis of molecular BRs over a decade ago, using a strategy whereby we attempted to slot the three rings together, one at a time, by successive templation events which depend upon highly controlled self-assembly processes wherein the molecular recognition between any pair of rings is orthogonal in nature.[2, 4] The strategy was only partially successful. While it was not too difficult to fit one ring inside another, the introduction of the third ring with the appropriate topology in relation to the other two rings could not be achieved come what may by us – or indeed by others, as far as I know. We, therefore, abandoned this synthetic strategy in favor of one which relies upon a strict self-assembly protocol to bring the components of three identical rings together in one step under template-directed control.[3] This all-in-one strategy combines all the virtues of reversibility,

proof reading and error checking that we associate with supramolecular and dynamic covalent chemistry,[5] not to mention the geometrical precision afforded by dynamic coordinative chemistry. It allows the synthetic chemist to run the gauntlet of assembling molecular BRs using transition metal templates to direct the formation of macrocyclic ligands which can be guided covalently with the aid of multiple stabilizing noncovalent bonding interactions under both kinetic and thermodynamic control. Such a paradigm requires that each individual step in the molecular self-assembly process is programmed so that the panoply of stabilizing interactions between the components in the growing product is optimized in a highly cooperative manner. A good dose of intuition and computer molecular modeling were employed by Stuart Cantrill and Anthony Pease in the design of the BR^{12+} dodecacation shown in Figure 1.

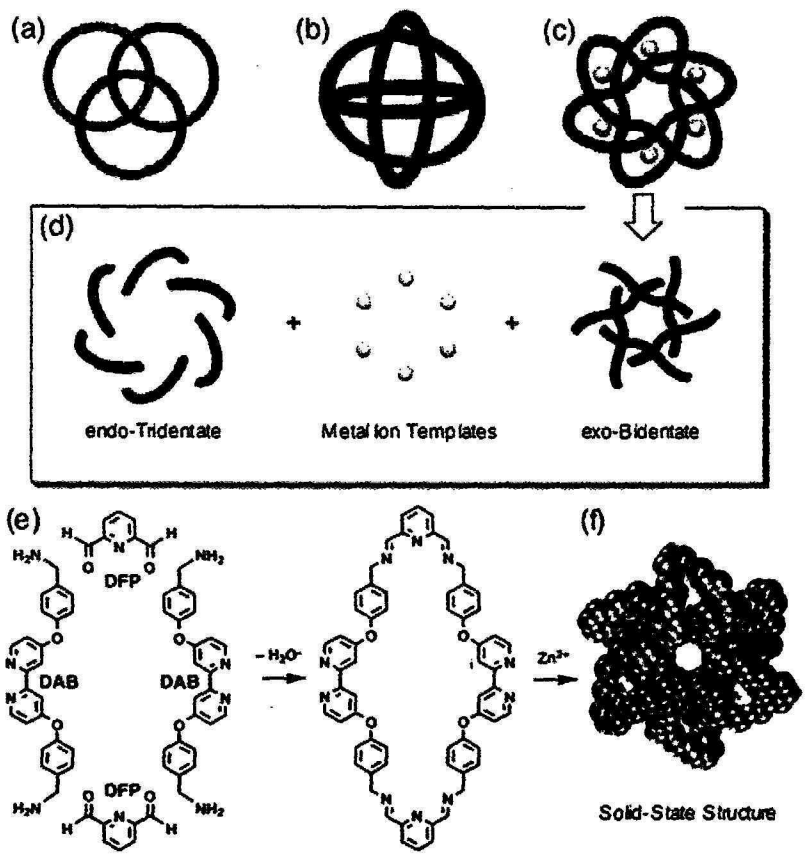


Fig. 1

The self-assembly of this dodecacation, which is topologically achiral, from 18 components by the template-directed formation of 12 imine and 30 dative bonds associated with the coordination of three identical mechanically interlocked macrocycles, each tetranucleating and decadentate overall to a total of six zinc (II) ions, was achieved by Kelly Chichak in near quantitative yield, using the conditions summarized in the caption to Figure 1. The three identical macrocycles present diagonally in pairs, six *exo*-bidentate bipyridyl and six *endo*-tridentate diiminopyridyl ligands to six zinc (II) ions. The $\mathbf{BR}^{12+}$ dodecacation, which was fully characterized by mass spectrometry (MS) in the gas phase, by ^{1}H nuclear magnetic resonance (NMR) spectroscopy in solution, and by X-ray crystallography of a suitable single crystal in the solid state, constitutes an organometallic nanoparticle with an approximate diameter of 2.5 nm and an inner chamber of volume 250 $Å^3$ lined with 12 oxygen atoms. In a recent review, Daryle Busch, the father of templation in chemistry has commented,[6] as follows, on our synthesis of the $\mathbf{BR}^{12+}$ dodecacation –

> *"The achievement was remarkable in a number of ways. It involved what is probably the most complicated template in the chemical literature, based on six zinc(II) ions and both convergent (or endo-directed) and divergent (or exo-directed) molecular turns. In contrast to the overall complexity of the templating system, the reactants were relatively simple. The divergent component was a dipyridyl while the convergent component was an a,a'-diiminopyridyl unit formed by a thermodynamic, or equilibrium, templating process. Top of the outstanding characteristics of the template is the fact that it involves both kinetic and thermodynamic template components, a combination that should become common. Both of these distinctive template types were used in their fully modern contexts. The combination is extremely powerful; the components of the kinetic template hold the subjugated components in place while the thermodynamic components find their final disposition at equilibrium. In the classic equilibrium template the reactants form their normal distribution of products and the anchoring/selecting factor (often a metal ion) selects the product that binds best, combines with it and shifts the equilibrium accordingly. Only the authors know the extent to which alternative components were selected and rejected in failure, but their final choices contain still another special feature. The choice of zinc as the template anchor provided a second opportunity for flexibility in the reacting system because*

zinc, being a spherical ion, is adaptable when it comes to coordination numbers and coordination geometries. So, this template system allowed the chemistry to determine critical features both in the Schiff base reaction steps and in the basic stereochemistry of the metal ion anchor. Further, the yield in this scientific triumph was 90%. The success over the enormous challenge of synthesizing the molecular embodiment of the Borromean link suggests that the science of using the molecular template has reached a level of maturity from which scientists may be expected to produce new molecular entanglements and interlocked structures of profound significance, despite the equally profound challenges they represent."

Let me just add that the progression from design to synthesis was seamless – an extremely rare occurrence in any total synthesis in my experience. It is the template-directed protocol, working in chemical synthesis with such a vengeance, that tells us that much more is possible. The making of the molecular BRs by supramolecular assistance to covalent synthesis[7] heralds the beginning of a new era in topological chemistry.

By employing atom labels (Cl and Br) on one of the ligands precursors, the lability of at least some of the 30 dative and 12 imine bonds stabilizing and constituting the three rings of the metallo-Borromean linked compound have been scrambled in acidic methanol solution, i.e., Kelly Chichak demonstrated[8] that the molecular Borromean links are indeed dynamic.

The purists could argue that, until we have removed the zinc (II) ions from the metallo-Borromean-linked compounds, we do not have nanoscale BRs for real. Indeed, Andrea Peters has shown[9] that borohydride reduction of the parent Borromean-linked complex, containing six zinc (II) ions and 12 imine bonds, results in its demetallation, producing a neutral Borromean-linked compound and also its free macrocycle, following cleavage of at least one of the imine bonds in an ethanolic reaction mixture, i.e., we were presented with the intellectually satisfying chemical proof of the topology as a bonus in this investigation!

When something new happens, there is inevitably a naming opportunity and we have accorded ourselves this prerogative. Following in the wake of Lehn's 'cryptates' and 'cryptands', and Sauvage's 'catenates' and

'catenands', we have proposed[9] the use of the terms 'Borromeate' and 'Borromeand' for the metallated and demetallated analogues, respectively.

In our initial experiments that led[3] to the production of the BR^{12+} dodecacation, we had chosen zinc (II) as the metal template for two reasons. Firstly, it is kinetically labile and so accommodates the octahedral geometry required six times over in the formation of the BR^{12+} dodecacation. Secondly, it is diamagnetic, a property which makes it possible to monitor reactions by ^1H NMR spectroscopy. Kelly and Andrea went on subsequently to synthesize a range of Borromeates, e.g., $BR\text{-}Cu_6^{12+}$ (85%), $BR\text{-}Ni_6^{12+}$ (82%), $BR\text{-}Cd_6^{12+}$ (80%), $BR\text{-}Mn_6^{12+}$ (70%), and $BR\text{-}Co_6^{12+}$ (36%) using other transition metal ions as templates. I was a little taken aback when Cari Pentecost told me she was going to mix metal templates – zinc (II) with copper (II) to be precise – in a 1:1 ratio, while otherwise using exactly the same conditions as those employed in the making of the $BR\text{-}Zn_6^{12+}$ dodecacation. Although it is known that mixed metal templates can result in the production of metallo-organic architectures different from those that are templated by their homometal analogues, I was skeptical of the outcome. A surprise, however, was in store for me because crystallization of the crude product isolated from the reaction mixture during a two-week waiting period afforded[10] single crystals suitable for X-ray crystallography. The solid-state structure revealed they were not composed of molecular BRs but rather of two of the very same macrocycles mechanically interlocked with the topology of a Solomon knot (SK). This finding is significant because it suggests that, in these dynamic mechanically interlocked systems, there is present, under the appropriate conditions which involve the judicious choice of counterions and solvents as well as a preparedness to be patient, a dynamic combinatorial library of compounds from which it is possible, during a kinetically controlled crystallization process, to amplify (Figure 2) one of the members of the library – namely, a molecular SK.

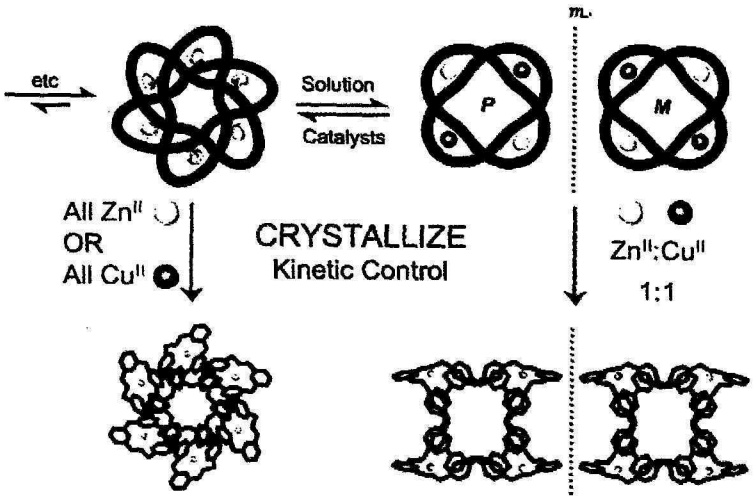
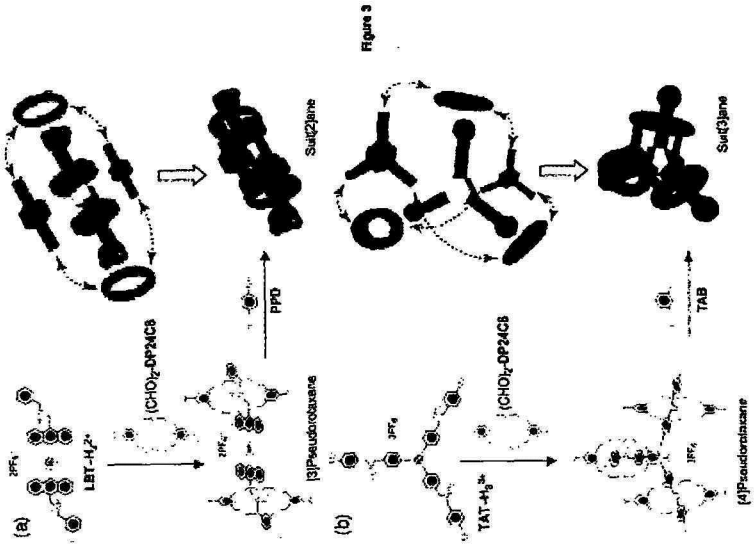


Figure 2

We have carried the reversibility[5] of imine bond formation (and hydrolysis) over into the making of a new class of mechanically interlocked molecules called suitanes.[11] They consist of a rigid 'body' composed of two or more 'limbs' that extend outwards from within a close-filling, all-in-one 'suit' wrapped around the 'torso' of the 'body'. A digit, surrounded by square brackets, is inserted between 'suit' and 'ane' in suitane to indicate the number of 'limbs' attached to the 'torso.' Thus, a suit[2]ane is composed (Figure 3a) of a rigid linear 'body' with two 'limbs' oriented in opposite directions from each other that is enclosed within a tight-fitting 'suit', such that there is no way of removing the 'suit' from the 'body' without breaking covalent bonds. Likewise, suit[3]ane (Figure 3b) and suit[4]ane consist of 'bodies' with three and four 'limbs', respectively, that are trigonal (120°) and square (90°) planar and ready to be filled out with the appropriate 'suits' containing three and four holes, respectively.



The molecular recognition motif that Avril Williams, Jovica Badjic, Fabio Aricó and Brian Northrop have employed to make suitanes depends on the strong hydrogen bonding interactions that occur between macrocycles with the [24]crown-8 constitution and dibenzylammonium ion centers.[12] The template-directed synthesis (Figure 3) of both suit[2]ane and suit[3]ane, using this recognition motif in conjunction with reversible imine bond formation,[5] have been achieved[11] with considerable ease. Space-filling representations of the two products are shown in Figure 4. The suit[2]ane (Figure 4a) is represented as a solid-state structure, whereas the suit[3]ane (Figure 4b) is displayed as a space-filling model resulting from molecular force-field computations. These molecular structures may be looked upon as prototypes for the design and synthesis of artificial assemblies reminiscent of living cells.

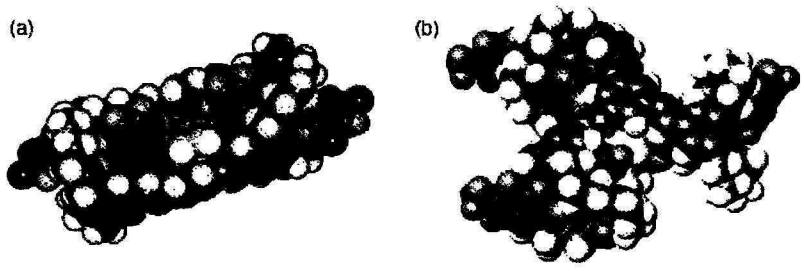


Figure 4

By focusing at the outset on suitanes, not to mention molecular BRs and SKs, I have selected the most recent of the expanding palate of mechanically interlocked molecules, of which the so-called catenanes and rotaxanes are the archetypal examples.[1] Catenanes (from the Latin *catena* meaning chain) are composed of two or more mechanically interlocked rings in a chain-like manner, whereas rotaxanes (from the Latin *rota* and *axis* meaning wheel and axle, respectively) contain a linear dumbbell-shaped component – comprised of a central rod section terminated by bulky end-groups or stoppers – around which one or more rings are trapped in an abacus-like manner. A digit, enclosed inside square brackets, as a prefix to either of these molecules – e.g., [2]catenane or [3]rotaxane – indicates the total number of molecular components making up the mechanically interlocked molecule, viz., a [3]rotaxane has two rings trapped on one and the same dumbbell. No longer esoteric curiosities, [2]catenanes and [2]rotaxanes that display bistability are now being explored as prototypical molecular switches[13] and machines[14] – both functions that arise with the ability to control the relative circumrotations and/or translations of the mechanically interlocked components in the molecules on demand.

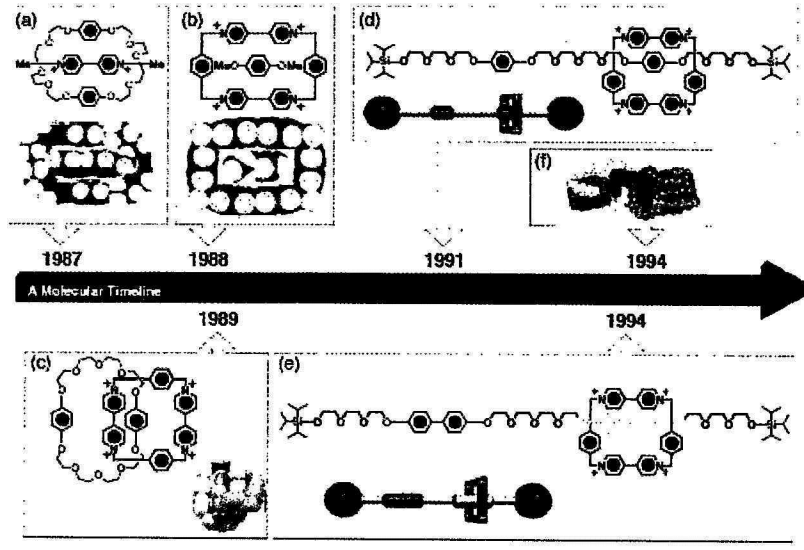


Figure 5

Our realization of a molecular switch in a device setting was the culmination of a long period of fundamental research with a timeline (Figure 5) that began in 1987 with the observation[15] of the formation (Figure 5a) of a 1:1 complex between a π-electron-rich crown ether, bis-*p*-phenylene[34]crown-10, and the π-electron-deficient, paraquat (methyl viologen) dication. This donor/acceptor recognition motif was expressed (Figure 5b) three years later the other way round when the π-electron-deficient tetracationic cyclophane, cyclobis(paraquat-*p*-phenylene), was found[16] to form a 1:1 complex with 1,4-dimethoxybenzene, and many more π-electron rich guests. These observations led[17] in 1989 to the template-directed synthesis under kinetic control of the first (degenerate) donor/acceptor [2]catenane (Figure 5c) in 70% yield by Neil Spencer and Christina Vicent. Soon thereafter, Pier-Lucio Anelli made the first (degenerate) [2]rotaxane which we called a molecular shuttle (Figure 5d) when we published his triumph as a communication[18] in the *Journal of the American Chemical Society* in 1991. In the concluding paragraph of this short paper, we commented –

> *The molecular shuttle..... is the prototype for the construction of more intricate molecular assemblies where the components will be designed to receive, store, transfer, and transmit information in a highly*

controllable manner, following their spontaneous self-assembly at the supramolecular level. Increasingly, we can look forward to a bottom up approach to nanotechnology which is targeted toward the development of information processing systems.

Three years later in 1994, working in collaboration with Angel Kaifer at the University of Miami (we were prevented by this time to use benzidine in a research laboratory in the UK), Richard Bissell brought the first of many bistable redox-controllable [2]rotaxanes into being (Figure 5e). Our article[19] in *Nature* was to herald the beginning of our own research, not only into molecular switches, but also into artificial molecular machines.[14] In the intervening years, this area has burgeoned into a major field of research.

We have never, knowingly at least, forgone the opportunity subsequently to demonstrate the potential of template-directed protocols in synthesis to further the chemistry of the mechanical bond, be it under kinetic or thermodynamic control. The emergence (Figure 5f) of a [5]catenane[20] in the expert hands of David Amabilino – and subsequently a branched [7]catenane[21] thanks to the talent of Ju-Young Lee – in the donor/acceptor series of mechanically interlocked molecules was made all the more real for us as a result of two X-ray crystal structures obtained by David Williams at Imperial College London. He deserves much of the credit for bringing our molecules – hundreds of them during more than 30 years in fact – to life in a way that only solid-state structures can in the area of structural characterization.

The one property of the original (degenerate) [2]catenane and [2]rotaxane (molecular shuttle) that really did excite me was the fact that the noncovalent bonding interactions accumulated within the molecules during their templated syntheses live on inside them afterwards. This characteristic behavior was self-evident from the ^{1}H NMR spectra recorded on their solutions, as well as from their solid-state structures where π-π stacking interactions are seen to be dominant. The first example (Figure 6) of a bistable [2]catenane[22] was designed and synthesized by Gunter Mattersteig (Figure 6c/d). He replaced one of the two hydroquinone rings in the crown ether component of the original [2]catenane (Figure 6a/b) with a tetrathiafulvalene (TTF) unit and the other one with a 1,5-dioxynaphthalene (DNP) unit. Gunter based his design on an observation[23] made by Douglas Philp – namely, that TTF, of all the π-donors hosted by cyclobis(paraquat-*p*-phenylene), was by far the most tightly bound within its cavity, and certainly much more so than

1,5-dimethoxynaphthalene. The fact that the TTF unit can be oxidized chemically or electrochemically to both its radical cation and dication in a reversible fashion allowed us, in collaboration with Vicenzo Balzani and Alberto Credi at the University of Bologna, to switch[24] Gunter's bistable [2]catenane back and forth between a green ground state and a purple metastable state. About the same time, Francisco Raymo, in collaboration with Masumi Asakawa in the Nanoarchetectonics Research Center in the National Institute of Advanced Industrial Science and Technology at Tsukuba in Japan went on to show[25] that, if the four hexafluorophosphate counterions associated with the bistable [2]catenane were exchanged for dimyristoylphosphatidyl ($DMPA^-$) anions, then stable monolayers of the tetracationic [2]catenane could be obtained (Figure 6b) at the air-water interface using a Langmuir trough. The area occupied by each bistable [2]catenane tetracation was found to be just a little over one square nanometer. In other words, at around one cubic nanometer in size, Gunter's bistable [2]catenane constitutes the smallest molecular switch we have made to date. Our expertise in the production of Langmuir monolayers had been gained in the beginning when Jon Preece spent a period in the mid-1990s in Helmut Ringsdorf's laboratories at the University of Mainz putting the original (degenerate) [2]catenane through its paces (Figure 6c) on a Langmuir trough.[26] This research was to have its importance realized later on at the University of California, Los Angeles (UCLA) when I began a collaboration after I had moved there in 1997 with Jim Heath in the area (Figure 6g/h) of molecular electronics.[27]

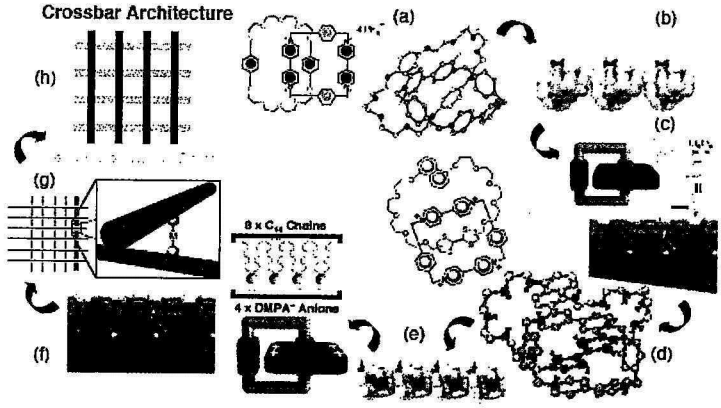


Figure 6

Although much of the initial research carried out at UCLA by Jan Jeppesen and Kent Nielsen from Jan Becher's group at the University of Southern Denmark in Odense on switchable bistable [2] catenanes and [2]rotaxanes was performed[13] in the solution phase, we have demonstrated[28] during the past four years that the relative mechanical movements between the components of these mechanically interlocked molecules can be stimulated[29] (1) chemically in condensed phases, including Langmuir films and Langmuir-Blodgett monolayers, (2) electrochemically in a highly viscous polymer matrix and also as a self-assembled monolayer on gold (half device), and (3) electronically within solid-state molecular switch tunnel junctions (MSTJs) (full device). Not only has reversible, electronically driven switching been observed (Figure 7) in full devices incorporating a monolayer of bistable [2]catenane tetracations accompanied by their supporting $DMPA^-$ counterions (Figure 7b) sandwiched between a bottom polysilicon electrode and a top titanium/aluminum electrode, but a crossbar random-access memory circuit and logic circuit have been fabricated[30] by the Heath group using amphiphilic, bistable [2]rotaxanes (Figure 7a).

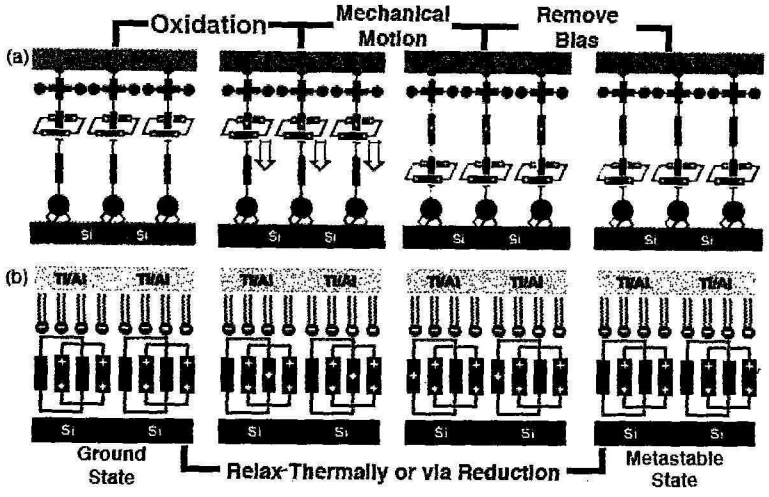
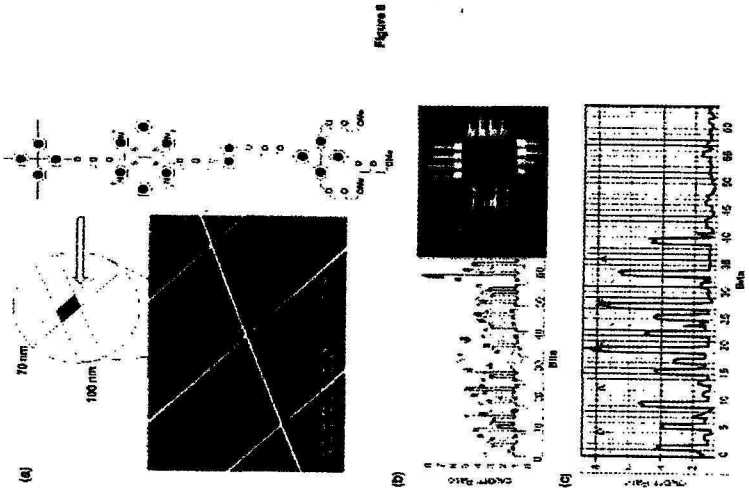


Figure 7

The experiments in the condensed phases, as well as in the half and full devices, provide[27] compelling evidence that the bistable [2]catenanes and [2]rotaxanes operate mechanically in a soft-matter environment and can withstand harsh device-fabrication steps. In close collaboration with David Steuerman in the Heath group at Caltech, Hsien-Rong Tseng,

Amar Flood, and Andrea Peters identified[31] by time-dependent cyclic voltammetry in solution at low temperatures, as well as in the polymer matrix and half device, a metastable state for the molecular switches where the cyclobis(paraquat-*p*-phenylene) ring resides on the DNP unit. In the full devices, this state is postulated to correspond to the closed or ON position (more conducting) of the switch. When the tetracationic cyclophane encircles the TTF unit (the ground state), the switch is in the open or OFF position (less conducting). First-principles calculations of the current/voltage responses, carried out in Bill Goddard's group at Caltech on model rotaxane systems of the metastable and ground states, support[13] their association with the ON and OFF positions, respectively, of the switch – and so lend support to the proposed switching mechanism in the full device. The metastable state of a switch in a full device decays back to the ground state during a period of 10-120 minutes. If, however, the bipyridinium units in cyclobis(paraquat-*p*-phenylene) are reduced from dications to cation radicals, molecular recognition is obliterated and the switch resets itself instantaneously. It transpires that the metastable to ground state relaxation times of the bistable molecular switches in solution are much shorter than they are in the polymer matrix and in the half device by at least an order of magnitude. By the same token the relaxation times in the full devices are longer than they are in the polymer matrix and in the half device by at least another order of magnitude. In terms of activation barriers, to get from the metastable back to the ground state, a value of around 16 kcal mol^{-1} in solution rises to around 18 kcal mol^{-1} in the polymer matrix and half device, and finally up to around 22 kcal mol^{-1} in full devices.[27]



The marriage between molecules and electrodes is a delicate one to perform and at the same time retain molecular signatures. While Jim Heath's group finds it possible to observe remnant molecular signatures for bistable [2]catenanes and [2]rotaxanes (Figure 8) trapped between a polysilicon bottom electrode and titanium/aluminum top electrode, the Hewlett-Packard (HP) group see no remnant molecular signatures when they replace the polysilicon bottom electrode in the crossbar device with platinum.[13] It seems that a totally different (physical) mechanism operates in this latter case: switching is of much higher amplitude, there is no activation barrier, and the switches are non-volatile. It is not unlikely that nanofilamentary growth is occurring in the HP full devices. Since silicon and oxygen (in polysilicon) provide the opportunity to reveal remnant molecular signatures in bistable [2]catenane and [2]rotaxane devices, we asked ourselves, what about carbon? Indeed, when a semiconducting carbon nanotube is chosen as the bottom electrode, a remnant molecular signature is observed in the appropriate devices. Thus, it seems as if carbon, silicon, and oxygen are all good choices for electrode compositions when carrying out molecular electronics with our bistable [2]catenanes (Figure 9) and [2]rotaxanes.

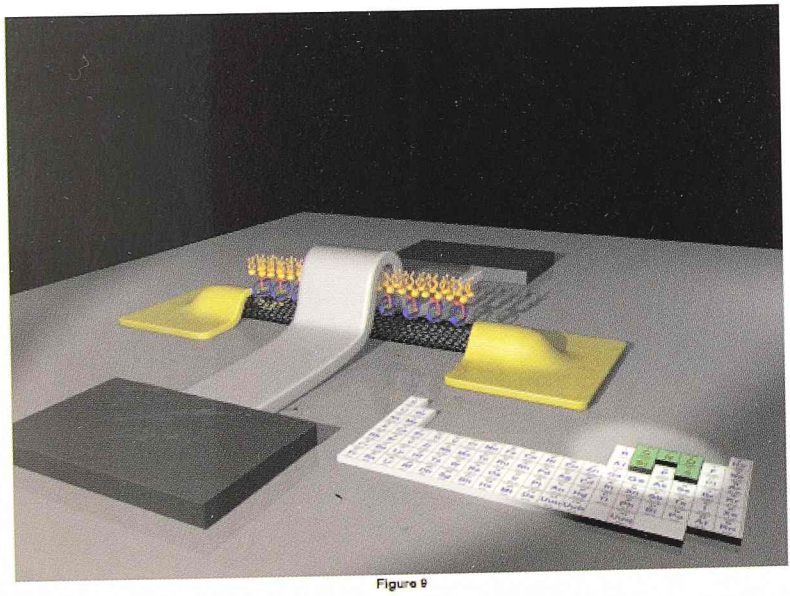


Figure 9

As far as the top electrode is concerned, titanium forms titanium-carbide bonds with alkyl chains in the exposed hydrophobic parts of the

molecular monolayers – $DMPA^-$ anions in the case of switchable [2]catenanes and the alkyl-substituted tetraarylmethane stoppers in the case of the switchable [2]rotaxanes. It would seem that our bistable organic molecules reveal their switching by an electromechanical mechanism[13] when, and only when, the electrodes are composed of elements (C, Si, O, and Ti) that are close to those (C, N, O, Si and S) present in the organic molecules themselves. Under such circumstances the work functions involving the electrodes and the molecules are very similar and so are a good match. Revealing the chemistry in such full devices is a delicate matter indeed.

Delicate or not, it has been possible[32] to assemble a crossbar memory consisting (Figure 10) of 400 Si bottom-nanowire electrodes (16 nm wide, 33 nm pitch) crossed by 400 Ti top-nanowire electrodes (16 nm wide, 33 nm pitch), sandwiching a monolayer of around 300 bistable rotaxane molecules. This 160,000-bit molecular electronic memory was fabricated at a density of 10^{11} bits per square centimeter, corresponding to the dimensions of a DRAM circuit projected to be available by 2020. The entire 160,000-bit crossbar is approximately the size of a white blood cell (~ 13 x 13 μm^2).

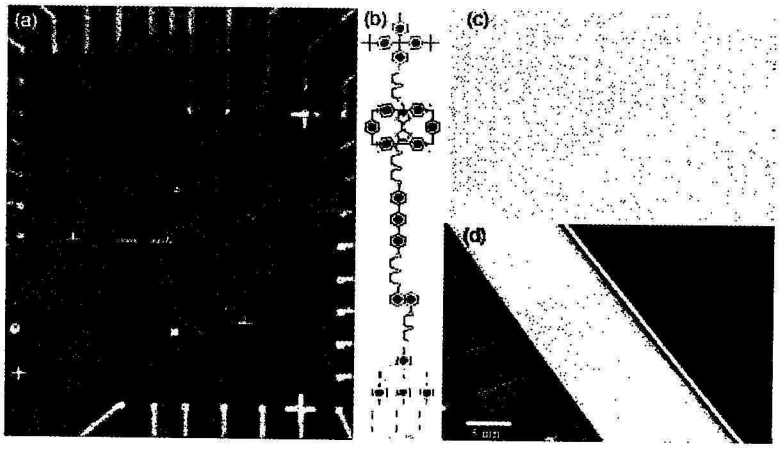


Figure 10

Nanotechnology needs chemistry in more ways than one as far as the making of smart devices is concerned. In order to impact molecular nanotechnology, the chemist needs to make significantly more complex molecules. The time is ripe for creative and efficient templated synthesis

to be supported by rapid and reliable analytical and physical measurements, as well as adventuresome and fearless computational work. The chemist needs to embrace the complexity that is associated with integrated systems and respond to their emergent properties in an all-encompassing manner.

Acknowledgements. I have only been able to relate the story told in this article because of the intimate involvement of hundreds of outstanding (post)graduate students and postdoctoral scholars who have contributed in large measure to my research group over the years – not to mention the support of a critical nature that flowed from Norma Stoddart, the matriarch of the research group. I would like to put on record here my thanks to her and to all of them together, along with countless collaborators the world over with whom I have had the pleasure of doing research at a range of levels and frequencies. I have been fortunate beyond belief to have lived in places and times when other people in the form of taxpayers and sponsors have chosen to support me financially and in other ways to practice my hobby every day of my life. I am indebted to countless sources for this largess and bounty.

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Professor Roshdi Hifni Rashed
Winner of the 2007
King Faisal International Prize for
Islamic Studies

Professor Roshdi Hifni Rashed's Contributions to the History of Science and Mathematics In Islam.

The King Faisal International Prize for Islamic Studies has been awarded this year to Professor Roshdi H. Rashed, an internationally renowned science historian and Honorary Distinguished Research Director at the French National Center for Scientific Research (CNRS). The following is a summary of his major contributions as outlined by the Director of the French National Center for Scientific Research (CNRS):

■ Professor Rashed was able to make a series of first-rate ancient Islamic scientific figures, such as *al-Samaw'al*, *Sharaf al-Din al-Tüsi*, *Ibn Sahl*, *al-Halabi*, among others, emerge from the shadows where they had been buried. The knowledge of their contributions has not only enriched the field of history of sciences in Islam, but has also deeply modified the conception historians had of them until then.

■ The second task he accomplished consisted in completing, specifying and deepening the knowledge we had of Muslim scientists who were already known, by means of new discoveries and by the systematic study of their various fields of activity. Thus, although the optical works of *Ibn al-Haytham* were known thanks to the magisterial book by Mustafa Nazif (1942) and the works of Wiedemann and many others, we had only a pale idea of the works of *Ibn al-Haytham* as a mathematician and an astronomer, until they were edited, translated, and commented on by Professor Rashed.

Likewise, Rashed's discoveries of works by al-Kindi on optics and mathematics, by *al-Fârisi* on mathematics and optics, by *Qusta ibn Liiqâ* on optics and mathematics, and so on, have enabled us to sketch a more accurate, and therefore more precise picture of the various scientific contributions of these great authors.

■ The third, and highly innovative, task of Roshdi Rashed was to go beyond merely individual contributions, in order to reconstitute the traditions of scientific research in which they take their place. This new methodology radically modifies the practice commonly utilized by historians of Islamic science. Thus, to study the work of *Ibn al-Haytham* on infinitesimal mathematics, Professor Rashed reconstituted the entire tradition in this field, beginning with the 9th century, with the *Banü Mflsâ*, *Thâbit ibn Qurra*, etc., down to *Ibn al-Haytham* himself. The

successive stages of this journey can be read in his four published volumes of Infinitesimal Mathematics.
Similarly, in order to understand *al-Kindi's* contribution to optics, he reconstituted all the works of the predecessors and contemporaries (Qusta ibn Luqa, for instance) of this philosophical mathematician. This same method of the reconstitution of traditions also presides over his work in other fields. From a history of individuals, which it had been previously, history of sciences in Islamic civilization thus found itself transformed into a history of scientific traditions.

■ The fourth task Professor Rashed set himself consisted in situating the scientific contributions of Islamic civilization, on the one hand with regard to Greek science, and on the other with regard to Latin science, and then to that of the 16th and 17th centuries in Europe. In order to realize this project, he first edited, translated, and analyzed a great many Arabic versions made from the Greek, of works that are often lost in their original language. It was thus that he edited, translated and commented on the Arithmetics of Diophantus of Alexandria, the Burning mirrors of Diodes, the Burning mirrors of Dtrüms, the Mechanical paradoxes of Anthemius of Tralles, the Burning mirrors of Didymus, and so on.

In addition, he has announced for the current year an edition, translation and commentary on the masterpiece of Apollonius, the Conics. As far as the Latin prolongations of Islamic science are concerned, Professor Rashed has written on Fibonacci, on the Latin readings of the book by the *Banü Miisâ*, on *al-Khayyâm* and Descartes, on Fermat and Ibn *al-Haytham*, and so on.

■ The fifth task, which followed quite naturally from his works and discoveries, has been to reconstitute the genuine research traditions that divide mathematical sciences in Islam: arithmetical algebra, algebraic geometry, infinitesimal geometry, geometry of transformations, the study of projections, new Diophantine analysis, combinatorial analysis, numerical analysis, and spherical geometry. In the other sciences, he distinguishes between anaclastics, geometrical optics, physical optics, and celestial kinematics.

This identification of traditions represents both a re—structuring of history of sciences, and a new "periodization". In an article which had considerable influence, Professor Rashed proposed to abandon the reductive old schemes and adopt a new, differential "periodization", which defines a category for each field, that of "classical science," This

new interpretative scheme for history of sciences has begun to be adopted by the most active researchers in the field.

■ The sixth task accomplished by Professor Rashed is multiform, and expresses his constant concern not to separate history of sciences from that of their applications. Thus, he as concerned himself with scientific instruments, on the level both of theory and of craftsmanship (the perfect compass, the great-circle compass, astrolabes, sundials, burning mirrors, lenses...). From this perspective, he has edited, translated, and commented on the works of such scientists as *Ibn Sinân, al-Quhi, al-Sijzi, Ibn al-Haytham*, which were devoted to these instruments, as well as the works some of them intended explicitly for craftsmen.

■ The seventh task was to show that this science and its exceptional development led to the elaboration of a philosophy of the sciences - in particular, a philosophy of mathematics - which proposes, alongside a new ontology, a new logic.

■ The eighth task, which has never ceased to be fundamental for Professor Rashed, has been to introduce the most rigorous criteria of philological and historical criticism into the field of the critical edition of scientific Arabic works.

■ The ninth task pursued by Professor Rashed consists in taking advantage of this new history of the sciences to reflect on what he calls "the history of applied sciences ", that is, to exploit the results obtained in order to think about the scientific modernization of Islamic nations. In this orientation, he has written on the subject of Iran, Egypt, and the Arab scientific community.

■ The tenth task, closely linked to the preceding one, was the exploration of a field of research he had designated as " Science and empires." The goal was to analyse, for the period of the great empires, what kinds of science were transmitted by colonial powers to their colonies, and then how, from this point, the possibility of scientific modernization had materialized in all these lands.