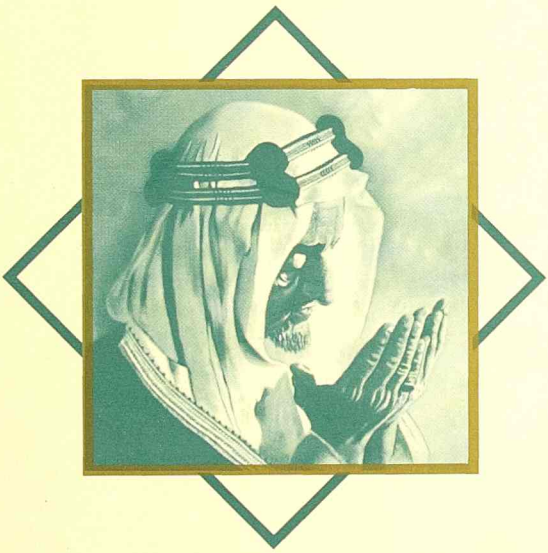
جائزة الملك فيصل العالمية
King Faisal International Prize



# ARTICLES IN MEDICINE AND SCIENCE II

## THE 2001 KING FAISAL INTERNATIONAL PRIZE

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Custodian of the Two Holy Mosques

**KING FAHD BIN ABD AL-AZIZ AL-SAUD**

Patron of King Faisal Foundation

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

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

Custodian of the Two Holy Mosques
King Fahd bin Abdul Aziz

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

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

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

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

# 2001 Prize Awards in Medicine and Science

The 2001 awards were presented in March 2001.

The Prize for Medicine (Organ Transplantation) was shared by Professor Sir Roy Calne of UK, and Professors Norman Shumway and Thomas Starzl of USA.

Professor Sir Roy Calne won the Prize in recognition of his pioneering research on the use of immunosuppressive drugs and other aspects of organ transplantation. Calne's experimental and clinical research on these drugs, has paved the way for heart, lung, liver, pancreas and kidney transplantation to become standard procedures throughout the world, thereby benefiting huge numbers of patients.

Professor Norman Shumway won the Prize in recognition of his major contributions which formed the basis of the initiation and establishment of heart and heart-lung transplantations as clinical therapies for patients with end-stage cardiac or cardiopulmonary disease.

Professor Thomas Starzl won the Prize in recognition of his pioneering work which has influenced all aspects of organ transplantation. Starzl was the first to develop successful surgical techniques for liver transplantation, and the first to introduce corticosteroids into clinical transplantation. He has also pioneered the use of FK506 to prevent the rejection of liver, small bowel, and multiple visceral organ transplants.

The Prize for Science (Physics) was shared by Professor Sajeev John of Canada and Professor Chen Ning Yang of USA.

Professor Sajeev John won the Prize in recognition of his major role in the elucidation of the basic principles of photonic band gap materials. This new technology, which involves the transmission of information by optical means, could eventually lead to the development of faster, cheaper and more versatile communication devices.

Professor Chen Ning Yang won the Prize in recognition of his profound contributions to physics and his part in the formulation of the non-abelian gauge theory (Quantum Yang–Mills Theory) that lays the foundation for the unification of all interactions in nature.

N.B. The 2002 Prize topic for Medicine will be "Pathophysiology of Chronic Heart Failure" and the 2002 Prize topic for Science will be "Mathematics".

# WINNERS OF THE 2001
# KING FAISAL INTERNATIONAL PRIZE
# FOR MEDICINE


# PROFESSOR SIR ROY Y. CALNE

## C0-Winner of the 2001 King Faisal International Prize for Medicine

**Photo**: Professor Sir Roy Y. Calne receives his prize from
HRH Prince Abd Allah ibn Abd Al-Aziz,
The Crown Prince, Deputy Chairman of the Council of Ministers
and Head of the National Guard

# SYNOPSIS OF ACHIEVEMENTS

Professor Calne's 42 years of research in transplantation started when he was a medical student; whilst caring for a youngster dying with kidney failure he realised that replacement of one of his diseased kidneys would have restored him to health. This was demonstrated in Boston about this time by Murray and his colleagues in kidney transplants between identical twins. The biology of rejection was discussed by Sir Peter Medawar, the acknowledged father of transplantation, in a lecture he gave in Oxford, and after that lecture Calne was resolved to work in this area. He taught himself the technique of experimental kidney transplantation and then investigated various methods of prolonging graft survival.

The first significant organ graft prolongation experimentally was achieved with the anti- leukaemia drug 6-mercaptopurine in 1959 and an attempt was made to use it in clinical practice by Calne and his colleagues in 1960. Collaborating with the Nobel Laureates Hitchings and Elion of Burroughs Wellcome, a number of substituted purines were investigated when Calne became a Visiting Harkness Fellow at the Harvard Medical School and the Peter Bent Brigham Hospital. One of the agents studied, azathioprine, proved to be superior to 6-mercaptopurine. This was used clinically at the Brigham shortly afterwards and when combined with corticosteroids, azathioprine was the start of successful kidney transplantation in humans where the donor was not a twin.

Borel's demonstration at the Sandoz laboratories of the immunosuppressive effect in vitro and on skin grafts in mice of the cyclic peptide cyclosporin led to experiments in Calne's lab which suggested that cyclosporin was much superior to previous methods of immunosuppression, and proved to be the case in clinical practice, although unexpected side effects were discovered when it was first used in man. However , when the dosage was reduced to a safe level, organ transplantation became widespread throughout the world and good results were obtained with heart, lung, liver and pancreas in addition to kidney transplants. Patients, however, still sometimes rejected grafts despite toxic doses of cyclosporin and the side effects of cyclosporin, steroids and azathioprine could all be harmful and distressing to patients.

The search continues for better immunosuppression and the use by Calne and colleagues of the monoclonal antibody Campath IH produced by Waldmann and colleagues in Cambridge has led to encouraging results in a small series of recipients with kidney transplants who have been maintained on half dose cyclosporin and no other immunosuppression for three years.

# ORGAN TRANSPLANTATION FROM THE LABORATORY TO THE CLINIC

**Sir Roy Y. Calne**

Emeritus Professor of Surgery, University of Cambridge,
U.K. and Yeoh Ghim Seng Professor of Surgery, National University of Singapore

My interest in transplantation began when I was a medical student taking care of a youngster about my own age with Bright's disease in Guy's Hospital where Bright had worked. I was told by the Senior Consultant that we would have to make him as comfortable as possible for the two weeks of life which remained. I asked if he could receive a kidney graft and was told no; I then asked why not, and was told, because it cannot be done. However, our group of students discussed the matter afterwards but there did not seem to be any information available. In fact we were wrong, because in the early 1950's a considerable amount of scientific work had already been done, particularly by Medawar and Gibson on the nature of rejection of grafts. Working in Glasgow in the 1940's they had shown that skin grafts in rabbits after initial vascularisation were destroyed by an inflammatory process and a second graft from the same donor was destroyed more quickly, revealing the immune nature of the graft rejection (1) (2) (3).

This was followed by similar experiments with kidney grafts by Simonsen in Denmark (4) and Dempster in England (5). It was only a few years later at the Peter Bent Brigham Hospital in Boston that Hume would report on the first functioning renal allograft in man (6) and Murray, Merrill and Harrison would begin their programme of identical twin renal grafts (7).

As far as I was concerned, that was the end of my initial personal probe into the subject and after serving in Hong Kong and Malaya in the Army, I returned to teach anatomy in Oxford and attended a science lecture given by Medawar in 1956 telling the exciting story of immunological tolerance, with beautiful illustrations. The lecture had the audience spellbound with brilliant oratory and the content of his message. At the end, a medical student asked if there were a potential application for this work; Medawar's reply was short -in fact two words, "absolutely none!". I was amazed that he felt this way, having seen photographs of black skin grafts on white mice and white feathers on black chickens.

However, I was able to start experiments of my own and found that total body x-irradiation was too toxic to be used to stop kidney graft rejection and I decided to use the anti-leukaemia drug 6-MP which Schwartz and Damashek (8) in Boston had shown prevented rabbits from producing antibodies. I started these experiments in the summer of 1959 and I was pleased to note that some of the

animals had prolonged renal allograft function. Mr. Watson, the Chief Technician, was particularly impressed since he had seen several hundred kidney grafts performed by Dempster and none had functioned as long as the grafts in the 6- MP treated dogs. This work produced a short paper which I submitted to the Lancet in November 1959, and it was published in the February of 1960 (9). I was lucky to be offered a post at Harvard Medical School and obtained a Harkness Fellowship.

On arrival in New York I took the train to Tuckahoe to the Burroughs Wellcome Laboratories to meet George Hitchings and Trudy Elion with whom I had corresponded. I could not have been received with more friendliness by these two great scientists, recipients of the Nobel Prize for Medicine in 1989. They had synthesized purine and pyrimidine analogues designed especially for the treatment of cancer. In the hope of finding a compound with a better therapeutic index than 6- MP , they gave me a number of purine and pyrimidine analogues to investigate.

BW57-322, an analogue of 6-MP, later known as Azathioprine (Imuran), seemed to be the best of these agents, a little superior to 6-MP (10,11). The high point of these experiments was the presentation at Grand Rounds at the Peter Bent Brigham Hospital of the first "patient" to survive a renal allograft, treated with Azathioprine with normal renal function at six months. After the case history had been read, the door was opened and my dog, Lollipop, pranced into the crowded auditorium, making friends with the distinguished professors in the front row. Shortly after this, the use of thipurines in clinical transplantation enabled the first phase of clinical organ transplantation to established with moderate success.

In 1965 I moved to the Chair of Surgery at Cambridge, where the prospect of renal transplantation was greeted with indifference or hostility by most of my new colleagues but supported by a few.

At about this time we heard of some liver grafting experiments performed in pigs by Terblanche (12) in Bristol and Garnier and Clot in Paris (13). I had not been involved in experimental liver grafting, although Dr. Francis Moore had carried out experiments developing the technique in the dog at the Brigham when I was there. We set about developing the technique of orthotopic liver allografting in the pig. This required much perseverance in the face of many disappointments but eventually we showed that liver grafts in the pig were rejected less aggressively than any other tissues and that a successful liver graft could make the animal tolerant to other tissue from the same donor, the first demonstration of an operational tolerance in immunologically mature, large animals without the use of immunosuppressive agents (14), findings more elegantly demonstrated by my colleagues Zimmerman, Kamada, Oavies and Roser (15) in liver grafts between different strains of rat.

Starzl did the first clinical liver transplantation in 1963 but the results were dismal (16). However, since we had now developed the technique and had

some information on the immunology of liver grafting in the pig, I felt that the time had come to embark on a clinical programme.

There was widespread opposition to this amongst my colleagues but a young adult with primary cancer of the liver was under my care and a child with mumps encephalitis was diagnosed as brain dead and his organs were offered for transplantation. Fortuitously on that day, Dr. Frances Moore was visiting his son who was a PhD student in molecular biology in Cambridge. He contacted me socially and when I told him of our possible liver graft, he came immediately to old Addenbrooke's Hospital. We gathered colleagues round in a circle and after the clinical presentation of the details of the potential recipient and donor I asked each in turn for their advice. They were unanimous in advising me against the liver transplant although each had a different reason. The last opinion I solicited was that of Dr. Moore, well-known even in Cambridge. He said "Roy, you've got to do it". This took the meeting by storm and we left immediately for the operating theatre. Dr. Moore was an enthusiastic first assistant for the first liver graft to be performed in Europe, which was technically successful, the patient surviving six weeks but ultimately succumbed to a lung infection. Since that day in 1968 we have done more than 1500 liver grafts with steadily improving results.

We continued to search for better methods of immunosuppression with an aim eventually to produce tolerance. After we had followed many leads with disappointment, in 1977 Jean Borel presented to the British Society of Immunology his experiments on the cyclic peptide Cyclosporin A (17). Dr. David White, an immunologist in my Department, thought this compound might have anitmacrophage activity and we were at that time interested in the macrophage. One of my visiting fellows, a Greek surgeon, Alkis Kostakis, learned how to transplant hearts heterotopically in rats and then started looking at conventional immunosuppressive drugs. Dr. White thought he might like to look at Cyclosporin A and some two months later he came to me very excited, explaining the wonderful results he had obtained with Cyclosporin A in prolonging heart transplants in the rat (18,19). We investigated Cyclosporin A in dogs with kidney grafts and in pigs with orthotopic heart grafts (20,21). We found that Cyclosporin A was far better than any other agent in both these models and proceeded to plan a pilot experiment for the use of Cyclosporin A in man (22,23).

To our intense worry, the early experience demonstrated a completely unexpected side effect of the drug in man, that of nephrotoxicity, which had not been observed in any of the animal experiments. Nevertheless, Cyclosporin A has made an important difference to the results of all organ grafting and has permitted for the first time successful transplantation of the heart with the lungs and enabled vascularised pancreas transplantation to develop as a useful therapy.

Immunological tolerance has been the goal of clinical organ grafting since the phenomenon was first described by Billingham and Medawar (24). Currently

powerful immunosuppressive drugs and antibodies are available; the early results of clinical organ grafting are good, but long-term functional graft survival is poor. Only 50% of cadaveric renal allografts surviving the first year are still functioning after 7.5 to 9.5 years (25). Chronic rejection is the main cause of graft failure. The general side effects of maintenance immunosuppression are infection and malignancy, especially lymphoma and skin cancer. Specific side effects of individual drugs include nephrotoxicity (Cyclosporin, Tracolimus); increased hair growth and gingival hyperplasia (Cyclosporin); cushingoid changes, stunting of growth, bone necrosis (corticosteroids); and bone marrow depression (Azathioprine).

Classic foetal tolerance cannot be applied clinically, but complete ablation of the reticuloendothelial system and repopulation of the bone marrow with well-matched donor bone marrow stem cells leads to tolerance in humans and to the danger of graft versus-host disease. A short course of cyclosporin accompanied by an infusion of donor bone marrow derived cells can result in tolerance of experimental renal allografts in pigs (26).

Knechtle and colleagues (27) have produced tolerance in a difficult rhesus monkey model using a powerful anti-CD3 monoclonal antibody linked to a modified diphtheria immunotoxin. Three doses of the immunotoxin were given intravenously, on three successive days, starting 7 days prior to renal transplantation. The total dose of 2 mg/kg given over the 3 days produced little toxicity, and tolerance was produced in most animals receiving mis-matched kidneys. Donor skin grafts were usually accepted long-term, but in one experiment the skin graft precipitated rejection of the "stable" kidney as well as the skin graft. The immunotoxin produced profound lymphocyte depletion, which was slow to recover; and it was postulated that depletion of T lymphocytes throughout the body was necessary in addition to purging the blood.

During clinical organ grafting there is a spectrum of immunological engagement, from tolerance to hyperacute rejection. Most patients with organ grafts require continuous dosage with immunosuppressive drugs. The objective is to shift the curve to the left so most patients are "operationally tolerant" or "almost tolerant" and require only minimal immunosuppression.

The requirements for tolerance are the best possible HLA match, minimum organ ischemia, and temporary destruction or inactivation of potential aggressive T cells. Current clinical protocols of immunosuppression probably do not achieve this aim.

Circulatory lymphocytes comprise less than 3% of the lymphocyte pool. Excessive and prolonged high dose immunosuppression may prevent the host-graft immunologic engagement necessary for tolerance and cause lethal infection or lymphoproliferative disease.

These and collateral observations support a hypothesis that in the absence of an aggressive T cell response an engagement of certain donor and recipient bone

marrow-derived cells can be beneficial, leading to tolerance. A window of opportunity for immune engagement (WOFIE) may be needed tor this to take place.

A humanised antibody produced in Cambridge with the unique target of CD52 is a powerful depletor of T and B lymphocytes and monocytes but not bone marrow stem cells (28). In view of the impossibility with cadaveric transplants of giving the antibody 7 days before grafting, a protocol was established that we investigated in 31 recipients of renal allografts; giving the antibody after allografting. These patients have been followed now for three years (29). No immunosuppression is given until the patient returns to the ward after the transplant operation. Then, with a preceding dose of intravenous hydrocortisone to control any cytokine release syndrome, the patients were given 20 mg of Campath IH intravenously. The following day a second and last dose was given. A period of 48 hours was then left without any immunosuppression, followed by daily Cyclosporin (Neoral) to achieve a trough blood level of around 100 ng/ml. No other immunosuppression was used unless there was evidence of rejection, in which case the patient was initially treated with three daily doses of Ig of prednisolone. If this did not rapidly reverse the rejection, the patients were managed with dual therapy of Cyclosporin and steroids. Infection prophylaxis was no different from standard management in our clinic.

At present, the mean follow-up is 3 years. All but one patient are alive and 28 have intact functioning grafts. There have been six separate episodes of steroid-responsive rejection. One patient has had a recurrence of her original disease. Two patients have suffered from opportunistic infections, which responded to therapy. One patient has died secondary to ischaemic cardiac failure.

These early results are encouraging. We have called the protocol "prope" tolerance, or "almost tolerance". Low-dose immunosuppression is the safeguard against acute rejection being precipitated by a viral infection or an allergy, and it provides the clinician with a safety net in that Cyclosporin is a standard drug and the dose can be increased if necessary. The advantages to this protocol are complete avoidance of steroids in most patients and considerable reduction in the cost of maintenance immuosuppression. One could argue that the Campath IH temporarily wipes out all circulating lymphocytes for approximately one month, leaving the "slate clean", and the slow recovery, particularly of CD4 cells, in the presence of an established graft can lead to some form of tolerance "mechanism(s)". We do not yet know the degree of lymphocyte depletion in lymphocyte depots scattered throughout the body; not do we have any data on the nature of the cellular response and cytokine production of lymphocytes when they return in the circulation, or of the behaviour of dendritic cells of the donor - nor for that matter whether there is any change in the presentation of donor antigens. Details of these questions are now being studied, including the kinetics of the immune recovery in these patients. A randomised trial comparing the above protocol with standard treatment is being planned.

## Future Prospects

The shortage of donors, increasing because of better results of organ grafts, is a central worry of all those involved in transplantation. There has been much work devoted to studying xenografting, that is transplantation from animals to man, but to date there has been no real successes in this area. We do not know if it is going to be possible to transplant organs successfully from animals to man, particularly the pig which is regarded by many as the most suitable donor. Concern has been expressed that endogenous virus present in pig cells might become a contagious disease in man and this has slowed progress in this area.

It would seem likely that cell transplantation will be the next major advance occurring at the same time as tolerance or prope tolerance becomes reproducible in the clinic. Results of islet transplants in Edmonton, Alberta, Canada for the treatment of diabetes have been very exciting and encouraging and point the way to future developments in the treatment of some serious and debilitating diseases (30). Diabetes and Parkinson's Disease are the most likely conditions to be treated successfully by cell transplants. Discussion of this area is outside the scope of the present article but there has been a remarkable increase in scientific literature suggesting that new concepts of cell differentiation and manipulation, exemplified in the cloning of "Dolly", may well lead to the development of cell banks. These could provide cells for transplantation and alleviation of patients with chronic diseases that so far have evaded treatment.

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# PROFESSOR NORMAN E. SHUMWAY

## Co-Winner of the 2001 King Faisal International Prize for Medicine

# SYNOPSIS OF ACHIEVEMENTS

Norman Edward Shumway is the Emeritus Frances and Charles Field Professor and Chairman of the Department of Cardiovascular Surgery at the Stanford University School of Medicine in Palo Alto, California. Upon his retirement in 1993, the Field Chair became the Norman E. Shumway Chair with Professor Bruce A. Reitz succeedjng to the chairmanship. Reitz, who trained at Stanford, was Chief of Cardiac Surgery at the Jobns Hopkins School of Medicine in Baltimore, Maryland from 1982 to 1992.

Shumway was born in Kalamazoo, Michigan in 1923. After one and a half years at the University of Michigan he entered the United States Army in March 1943. Basic infantry training was completed at Camp Wolters, Texas. Owing to the possible extended duration of the war, Shumway was among those who were returned to college for specialty training. After six months of engineering study, the results of an obligatory medical aptitude test sent Shumway to Baylor University in Waco, Texas for pre-medical study. Nine months later Shumway entered medical school at Vanderbilt University in Nashville, Tennessee, graduating in 1949.

Surgical training at the University of Minnesota fueled Shumway's interest in cardiac surgery. A Ph.D. was awarded in 1956 for research into open heart surgery under general hypothermia. In February, 1958 Shumway joined the surgical faculty at Stanford University as an instructor. Experiments were started with autotransplantation and allotransplantation of the heart in collaboration with Richard R. Lower who in 1965 joined David Hume in the Department of Surgery at the Medical College of Virginia in Richmond. The most important result of these experiments was to show that the orthotopically transplanted heart could function physiologically almost immediately.

Clinical heart transplantation was inaugurated at Stanford on 6 January 1968, and since that date some 1,100 patients have undergone transplantation with five year survival at 75%. In 1978 with cyclosporine, experiments in heart-lung transplantation were again studied using sub-human primates. Earlier canine heart-lung transplants were abandoned because of pulmonary denervation effects. Monkeys, like man, have in the floor of the 4$^{th}$ ventricle a respiratory center that permits essentially normal pulmoary function even in the presence of bilateral pulmonary denervation. After long term survival of the subhuman primate was accomplished, clinical application was commenced on 9 March, 1981. To date 320 patients have undergone heart-lung transplantation at Stanford with the 5 year survival approximately 45%. It should be noted that this was the first long term survival of any kind of pulmonary transplant.

Parri passu with thoracic organ transplantation was the exploration of use of the pulmonary valve as an autograft replacement for the mitral/or aortic valves. These experiments were reported first in 1960. The theory was that the pulmonary valve was expendable. Right ventricular outflow tract continuity was established by allograft aortae or dacron tubular grafts. Right ventricular dilatation soon followed, and clinical use of the pulmonary valve autograft awaited some kind of valvular reconstruction of the right ventricular outflow tract. This, then, represents the experimental basis for what is presently called the Ross operation, named after Mr. Donald Ross of London.

The most recent innovation in pulmonary transplantation at Stanford has been the lobar transplant from living and/or living related donors. Success elsewhere with hepatic lobar and pancreas transplants from living donors provided the background for this ultimate exploration and application of thoracic organ transplantation.

After 25 years of experiments, in August, 1984, a mechanical left ventricular substitute was implanted at Stanford as a prelude to heart transplantation. This was the first successful use of the mechanical heart as a bridge to transplantation. Additional refinements of the so-called Novacor left ventricular substitute continue to this day. Its permanent implantation is presently under clinical consideration. Incidentally, the patient operated upon in August, 1984 is alive and active some 16 years. post-transplant.

# THORACIC TRANSPLANTATION - THE STANFORD EXPERIENCE

**Norman E. Shumway**

Francis and Charles D. Field Emeritus Professor of Cardiothoracic Surgery, University of Stanford, California, USA

The dream of replacing severely diseased organs with healthy tissue from human and/or animal donors has its origins in antiquity. The heart and lungs comprised only a small fraction of that dream as recently as 50 years ago. Some experiments in heterotopic transplantation of the heart were attempted by Carrel and Guthrie at the University of Chicago in 1905[1] and by Frank Mann at the Mayo Clinic in 1935[2], but the problem of orthotopic transplantation of the heart was considered insurmountable. No experimental animal had ever survived after orthotopic allotransplantation of the heart.

Experiments with orthotopic heart transplants in the canine were started at Stanford in 1958. This work was begun in the then soon to be vacated laboratories of the old Stanford Lane Building in San Francisco. In late 1959 the Stanford University School of Medicine moved from San Francisco to the Palo Alto campus. Cass and Brock in London described similar experiments in 1959[3] but were unable to attain survival.

The general field of transplantation was beginning to show promise after the discovery of 6-mercaptopurine by Dameshek and Schwartz in 1959[4]. Except for renal grafts between identical twins there had been no significant success with clinical transplantation. Sir Roy Calne[5] and Charles Zukoski[6] showed extended survival of canine renal transplants using for the first time chemical immunosuppression with 6 mercaptopurine. Later Calne could demonstrate long term survival of renal grafts in dogs utilizing azathioprine, an analog of 6-MP[7]. The cork was out of the bottle. Medawar's elucidation of the immune reaction to transplanted tissue and Roy Calne's introduction of successful chemical immunosuppression paved the way for renal, hepatic, bone marrow and perhaps even cardiac transplantation.

In 1964[8] Hardy at the University of Mississippi transplanted a chimpanzee heart into a human recipient. There was no experimental evidence that any such transplant could succeed. Only Reemtsma's[9] moderate success with chimpanzee renal transplants in man could be cited as possible justification for the Hardy intervention. Nevertheless, it was the first human heart transplant using the Stanford surgical and preservation techniques.

By 1965 long term survival of the canine after orthotopic transplantation of the heart was reported. A special protocol of azathioprine and steroids was used. This success is reported by Richard Lower[10] at the annual meeting of the Society of University Surgeons. Rejection crises were identified by voltage decrements in the BKG, and now clinical trials awaited only adoption of the concept of brain death. Neurosurgeons of the day were slow to accept brain death despite elucidation of the Harvard criteria. It was common practice for the neurosurgical team to discontinue ventilatory support for the brain dead patient, continue rounds, return in 20 minutes when the heart had stopped, and declare the patient dead. Fortunately, this mentality slowly disappeared, and the clinical program in heart transplantation at Stanford began 6 January 1968. Since then some 1,150 patients at Stanford have undergone transplantation of the heart with five year survival at 75%.

Probably the most important discovery of all of the experimental studies at Stanford was the fact that there were no physiological barriers to orthotopic transplantation of the heart. The graft functioned almost perfectly almost immediately. Denervation and lymphatic interruption had no substantial effect on cardiac performance. Since that time (and even now to some extent) there was no satisfactory method for sustaining the patient if the transplant failed. Hypothermic storage of the heart was found to preserve myocardial integrity for periods up to seven[11] hours. Incidentally, cooling the heart became routine in all types of open heart surgery and extended the scope of surgical intervention to the most complex cardiac anomalies as well as valvular and coronary diseases[12].

The next important discovery in the laboratory was percutaneous transvenous endomyocardial biopsy developed by Caves and Billingham[13]. No one had ever considered actual biopsy of the heart transplant to assay its immunological status. Success with this technique was responsible for a significant increase in heart graft survival. Not only could the diagnosis of rejection be made precisely but the additional steroid given to treat rejection crises could be discontinued as the heart biopsy showed improvement. Rabbit antithymocyte globulin was introduced at this same time and was useful both to ameliorate rejection crises and for induction purposes.

In December, 1980 Stanford was privileged to use cyclosporine for the first time in clinical heart transplantation. The immunologic properties of cyclosporine were discovered by Jean Borel[14], and its experimental efficacy was determined by Roy Calne[15]. At the outset Calne used cyclosporine alone for renal transplantation. At Stanford cyclosporine was combined with steroid for heart transplants, but when the nephrotoxic effects of cyclosporine were documented, azathioprine was added in order to reduce the cyclosporine dosage. So-called triple therapy was designed with cyclosporine, azathioprine and steroid comprising the immunosuppressive protocol. Intravenous solumedrol was

reserved for rejection crises as identified by endomyocardial biopsy.
It is notable that the cyclosporine era could never have been without heart biopsy because the usual EKG effects of rejection seen with conventional immunosuppressive therapy were absent in the age of cyclosporine. The enormus advantage and benefit of cyclosporine therapy is seen in Figure 1. Lord Berkeley Moynihan, a renowned British surgeon, remarked that all of surgery could be divided into two periods, surgery before Lister and surgery after Lister. It is altogether appropriate that transplantation, not just the heart and lungs but all of transplantation, be divided into transplantation before cyclosporine and transplantation after cyclosporine.

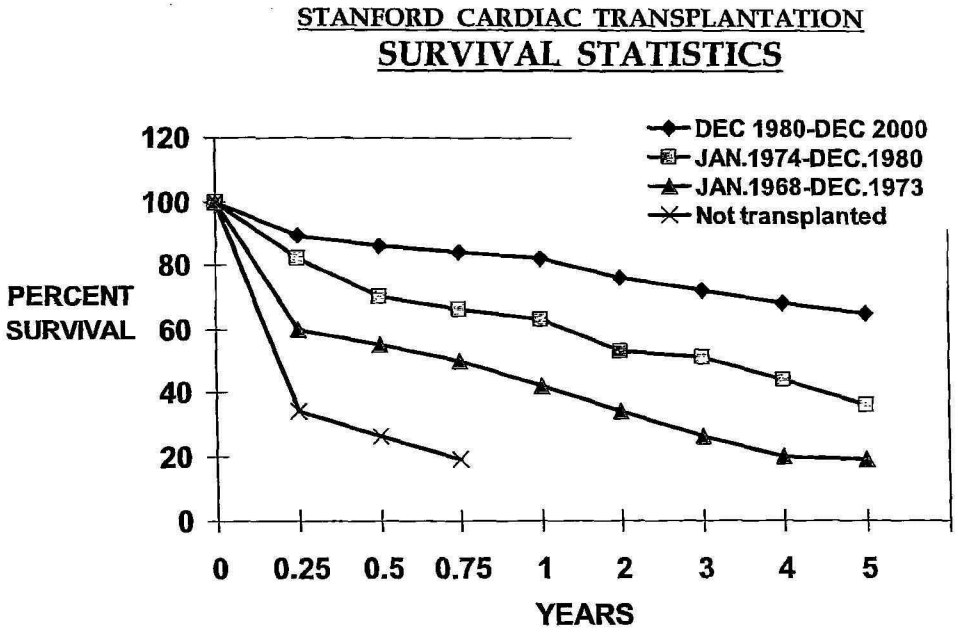


Figure 1: The striking increase in 5 year survival after heart transplantation is seen in this graph. All three curves contrast sharply with some 200 patients who were not transplanted owing to the donor shortage.

Cyclosporine has been responsible for two other important advances in thoracic transplantation. The first of these has to do with neonatal and pediatric heart transplantation. The steroid sparing effect of cyclosporine permits essentially normal growth and development of the neonate and/or pediatric patient. Prior to cyclosporine the larger doses of steroid resulted in both severe toxic effects and growth retardation. At the outset of neonatal heart transplantation, it was postulated that the relatively immature immune system would be more accepting of the graft, that the Medawar effect would achieve clinical validation. Almost the

exact opposite was found to occur. The human at the instant of birth has an immune system which is very much intact. Even with induction antithymocyte globulin, the neonate can reject lethally in the first ten days post transplant. Figure 2 shows survival rates for pediatric patients and adults.

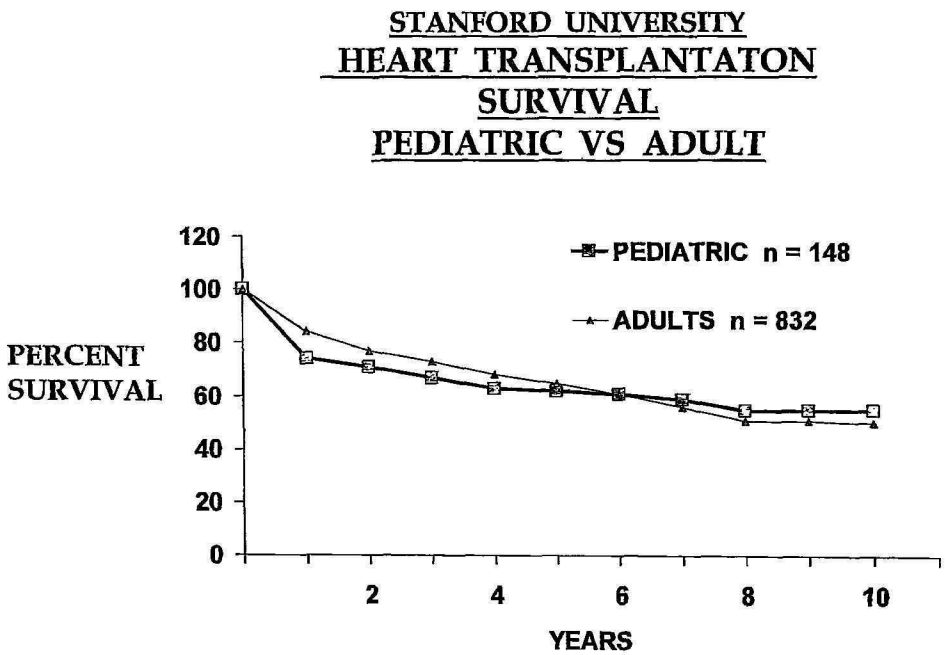


Figure 2: Little difference is apparent in the ten year survival between pediatric and adult patients after heart transplantation.

The second important dividend from the use of cyclosporine in thoracic transplantation was the first successful transplant of the heart with both lungs. This procedure was done at Stanford by Bruce Reitz[16] and John Wallwork after successfully transplanting the heart lung complex in sub-human primates, one of which lived 13 years, ten years without immunosuppression. The date for Reitz' clinical success was March 9, 1981. This transplant paved the way for lung, double lung and pulmonary lobar[17] transplantation.

Stanford studies with the artificial heart started in 1970. A left ventricular substitute was developed which was capable of flow rates equal to normal systemic output. In August, 1984 the Novacor left ventricular substitute provided a successful bridge to a heart transplant, and the patient is alive and active today some 16½ years later[18].

The future of transplantation depends on solution of the donor shortage. New immunosuppressive molecules have been very successful in prolonging graft survival with ever diminishing toxicity. There is today a strong movement to discontinue the use of both cyclosporine and Tacrolimus because of their severe nephrotoxic properties. It has been found that rapamycin, another potent immunosuppressive molecule, has little effect on the kidneys, so protocols are under development tbat will combine rapamycin with minimal dosages of steroid and perhaps some mycophenolate mofetil. Concordant xenografts have offered some hope in the donor shortage, but again donor availability and size are limiting factors. Discordant xenografts are under intense study, but so far results of pig to baboon orthotopic heart transplants have been poor. Thirty day survival is unusual. With genetic manipulation of the pig embryo only hyper acute rejection bas been consistently abolished. This was an important first step, but serious problems remain.

Progress with the artificial heart runs an almost parallel course with the xenograft objective. The artificial heart must await solution of the following obstacles: a totally implantable, inexhaustible, noiseless, non-heat producing power source and a long lasting, non-thrombogenic, non-hemolytic surface between the pump and blood. If valves are needed in the design of any such artificial heart, the ongoing search for the perfect heart valve replacement will proceed with renewed intensity.

The artificial lung presents even more obstacles and would seem to be an impetus to the use of more living and/or living related lobar donors.

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# PROFESSOR THOMAS E. STARZL

## Co-Winner of the 2001 King Faisal International Prize for Medicine

**Photo**: Professor Thomas E. Starzl receives his prize from
HRH Prince Abd Allah ibn Abd Al-Aziz,
The Crown Prince, Deputy Chairman of the Council of Ministers
And Head of the National Guard

# SYNOPSIS OF ACHIEVEMENTS

Born in LeMars, Iowa in 1926, Thomas E. Starzl received his B.A. in Biology with honor from Westminister College in Fulton Missouri in 1947. He joined the Northwestern University Medical College in Chicago, from which he received an M.A. degree in Anatomy in 1950 and a Ph.D. in neurophysiology as well as an M.D. in 1952.

Starzl's career in surgery and research began with an internship (1952-1953) and a fellowship (1953-1954) at the Johns Hopkins Hospital and University in Baltimore, followed by residencies at Johns Hopkins, the University of Miami, and the Veterans Administration Research Hospital in Chicago. He was a Markle Scholar in Medical Science and served on the faculty of Northwestern University Medical School from 1958 to 1961. He joined the University of Colorado School of Medicine as Associate Professor of Surgery in 1961, Professor in 1964 and Chairman of the Department of Surgery from 1972-1980. In 1980, he joined the University of Pittsburgh School of Medicine as Professor of Surgery, and was for ten years Chief of Transplantation Services at the Presbyterian University Hospital, Children's Hospital of Pittsburgh, and the Veterans Administration Hospital of the University of Pittsburgh (which has the largest transplant programme in the world). From 1991, he became Director of the University of Pittsburgh Transplant Institute, which was renamed in his honor in 1996.

Professor Starzl is one of the leading pioneers of organ transplantation. His landmark achievements in this field of medicine range from identifying better ways to control organ rejection to offering novel approaches to enhance understanding of the disease process. Having authored or co-authored more than 2000 scientific articles, four books and 292 chapters, he is one of the most prolific scientists in the world and the most cited one in the field of clinical medicine. He is also a member of more than 58 professional and scientific organizations, an elected President of the International Transplantation Society, a Founding President of the American Society of Transplant Surgeons and a Founding President of the Transplant Recipients International Organization. In addition, he is a member of the prestigious National French Academy of Medicine, a Fellow of the American Academy of Arts and Sciences and an Honorary Fellow of the Royal Colleges of Surgeons of England and Ireland, the Royal College of Physicians and Surgeons of Glasgow and the International College of Surgeons. He has given more than 1,200 presentations at major meetings throughout the world and is a member of editorial boards of 22 professional publications.

He received more than 175 awards including numerous prestigeous prizes in recognition of his outstanding contributions to the field of organ transplantation.

Professor Starzl's pioneering work has influenced all aspects of organ transplantation. He was the first to develop the surgical techniques without which successful liver transplantation would not have been possible and the first to introduce the important immunosuppressive drugs, corticosteroids, into clinical practice. He also pioneered the use of FK506 (tacrolimus) to prevent the rejection of the liver, small bowel and multiple

visceral organ transplants. Professor Starzl has also put forth some of the most challenging scientific concepts, such as transplant tolerance and microchimerism—the coexistence of donor and recipient cells—which stimulated much research and contributed significantly to the current understanding of transplant immunology.

Professor Starzl in currently Professor of Surgery at the University of Pittsburg School of Medicine and Director Emeritus of the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh Medical Center.

# THE BIRTH OF LIVER TRANSPLANTATION

**Thomas E. Starzl**

Professor of Surgery at the University of Pittsburgh School of Medicine and
Director Emeritus of the Thomas E. Starzl Transplantation
Institute of the University of Pittsburgh Medical Center

In the December 1963 issue of the journal, Surgery, Gynecology, and Obstetrics, I reported 3 clinical liver transplantations that had been attempted earlier in the year at the University of Colorado (1). The report was viewed by many with dismay, particularly because none of the patients survived for more than 3 weeks. The controversy was heightened by the fact that no organ other than the kidney had ever been transplanted previously to a human. Moreover, the prospects of further developing even the much simpler operation of renal transplantation seemed bleak at the time, making the liver trial seem to the most extreme critics like the height of folly.

Far from being capricious, these first liver transplantations had been preceded by 7 years of research involving liver preservation, techniques of hepatic and vascular surgery, and the physiologic interrelation of the liver with other intra-abdominal viscera. There were no means of preventing rejection at the time this work began. At the end, however, the decision to go forward with the human liver transplantations hinged on a strategy of immunosuppression developed by us in 1962 that immediately brought kidney transplantation to the level of a practical service, made liver transplantation feasible, and ultimately revolutionized the transplantation of all other organs.

## THE GENESIS OF THE IDEA
### Engraftment of an Extra Liver

The stages through which liver transplantation passed on the way to becoming the universally accepted court of last appeal for patients dying of end stage hepatic disease are summarized in Table 1 (1-47). The first recorded mention of hepatic transplantation in either the scientific or lay literature was in 1955, when C. Stuart Welch (Albany, NY) described the insertion of an auxiliary liver into the right paravertebral gutter of mongrel dogs (2). It was then thought that the critical hemodynamic determinant of normal hepatic homeostasis was the volume rather then the quality of blood delivered to the liver through its double blood supply (i.e. hepatic artery and portal vein). Consequently, when his auxiliary allografts were revascularized with a portal venous inflow from the host inferior vena caval blood, and the transplanted livers rapidly atrophied, Welch incorrectly ascribed the liver shrinkage to rejection.

## The Relevance of Hepatotrophic Factors

In the meanwhile, at the University of Miami where I was a surgical resident between 1956-58, I had developed non-transplant dog models with which to test my hypothesis that the liver and pancreas modified each other's structure and function. The first evidence supporting the possibility of such cross-modulation came from studying the effect on insulin and carbohydrate metabolism of altering portal venous inflow. The quality and quantity of the hepatic blood flow was modified by performing classical Eck fistula (end to side portacaval shunt) and reverse Eck fistula in normal dogs and in dogs with alloxan diabetes (48). In the course of the metabolic studies, the experimental procedure of total hepatectomy was developed (49). It was the first stage of orthotopic liver transplantation (liver replacement).

The circumstances in Miami precluded further development of the project. However, host hepatectomy followed by orthotopic liver transplantation was performed in dogs at an experimental laboratory of the Veterans Administration Research Hospital within a few days after I moved from the University of Miami to Northwestern University (Chicago) in late June 1958. Liver replacement was performed once or twice/week throughout the rest of the summer. The poor performance of orthotopic livers that were not revascularized with portal venous return from the pancreas, intestine, and other intra-abdominal organs (5) was explained by the transplanted liver's lack of access to a postulated factor present in high concentration in normal portal venous blood. The acute atrophy of Welch's auxiliary hepatic grafts was consistent with this reasoning. The "hepatotrophic factor" was suspected to be the endogenous insulin delivered to the portal vein in the venous effluent of the host pancreas (13).

Proving the insulin hypothesis and convincing skeptics that insulin was a true hepatic growth factor required nearly 15 years (24). When this finally was accomplished, a precise explanation could be provided for the necessity of revascularizing the tranplanted liver with splanchnic venous blood. More importantly, the previously enigmatic pathophysiology of Eck's fistula was clarified, including the development of hepatic encephalopathy. Eventually, the identification of a family of factors with insulin-like hepatotrophic properties that controlled liver structure, function, and the capacity for regeneration defined the new field of hepatotrophic physiology (50).

## Orthotopic Liver Transplantation

In 1956, Jack Cannon of the University of California, Los Angeles was the first to report experimental liver replacement, citing Welch's article or auxiliary liver transplantation as the stimulus for his work. Although the animal species was not stipulated in his untitled one page article, Cannon alluded to "several successful operations" . . . "without survival of the patient" (presumably dogs); no other information was given (3).

Definitive studies of canine liver transplantation were performed by us at Northwestern University (5) and independently by the team of Francis D. Moore at the Peter Bent Brigham Hospital ("The Brigham", Boston) (4). Because effective immune suppression was not yet available in either laboratory, it was possible to do little more than develop the operation and study the events of unaltered rejection. Between 1958 and early 1960, I carried out 80 of these hepatic replacement procedures in dogs (5,51) and 31 more were reported from Boston (4). All animals with > 4 day survival had histopathologic findings of allograft rejection.

The technical principles that emerged from this collective experience were: 1) the need for the transplanted liver to be nourished with venous blood returning to the heart via the portal vein from the other abdominal organs, 2) core cooling of the allograft by infusion of chilled solutions into the portal vein as is practiced clinically today, and 3) decompression of the occluded splanchnic and systemic venous pools into the upper vena caval system during the time the native liver was replaced with the allograft. The venous decompression was accomplished with a temporary external venovenous bypass. In addition to liver transplantation alone, modifications had been added by the end of 1959, including the multivisceral engraftment procedures (6,7) that would be used successfully in patients 3 decades later with essentially no change (8).

## A MOVEMENT TO THE CLINIC
## The Advent of Immunosuppression

Total body irradiation (TBI) (52), adrenal cortical steroids (53,54), and the myelotoxic drug 6-mercaptopurine (6-MP) were shown between 1953-1959 (55-57) to modestly prolong skin allograft survival in rabbits. Using TBI, successful kidney transplantation from fraternal (dizygotic) twin donors was accomplished at the Peter Bent Brigham Hospital (Boston) in January, 1959 and again 5 months later in Paris. Although the genetic barrier to transplantation finally had been breached in humans, liver transplant operations still had no conceivable application. Preoperative conditioning of dog liver recipients with TBI in our hands precluded even perioperative, much less extended, survival (58).

The drug 6-MP and subsequently its analogue, azathioprine, were viewed in a different light than TBI. Whereas kidney transplantation with survival exceeding one month had never previously been achieved with irradiation in mongrel dogs, the Englishman, Roy Calne (59) and the American Charles Zukoski (60) independently accomplished this objective with 6-MP in 1960. For the first time, the possibility of exploiting hepatic replacement to treat human liver disease could be envisioned as more than a fantasy.

Human liver transplantation was settled upon as a high priority during my discussions in June, 1961, with William R. Waddell, who had left the Massachusetts General Hospital to assume the chairmanship of surgery at the

University of Colorado. Five months later, I moved from Chicago to Denver to join Waddell. My new appointment was Chief of Surgery at the Denver Veterans Administration Hospital. Waddell and I agreed that a prerequisite for developing a human liver transplantation program would be establishment of a track record in clinical renal transplantation.

We had no illusions about the difficulty of this first step. In the United States, human kidney transplantation was under formal development only at the Peter Bent Brigham Hospital in Boston (Joseph Murray) (61,62). A program opened in 1960 by Willard Goodwin in Los Angeles had been closed in 1961 after the death of 6 consecutive recipients (63). We were aware that David Hume was planning to open a kidney center at the Medical College of Virginia, but this did not take place until near the end of 1962 (64).

Our clinical plans for both kidney and liver transplantation were shelved in January 1962. We had been following the tracks laid by the Boston kidney transplant pioneers and those in Paris (Rene Kuss and Jean Hamburger), only to eventually recognize that the enthusiasm initially generated by 6-MP and azathioprine was unwarranted. Calne had moved from London to Boston in June 1960 to collaborate with Joseph Murray in preclinical studies of the canine kidney transplant model (65,66). It had become clear in several surgical research laboratories including ours that survival for as long as 100 days after kidney transplantation in dogs was being achieved in less than 5% of experiments.

Calne and Murray recognized the unacceptable therapeutic margin of azathioprine alone, and had systematically tested drug combinations in their dog model. When prednisone given from the time of operation had no additive effect (65,66), they settled for clinical use on a triple drug cocktail of azathioprine, azathioprine, and actinomycin C. The results in the Boston trial of kidney transplantation were little different than with TBI. Of the first 10 human kidney recipients treated with drugs alone, only one survived for more than 6 months (62,67).

In fact, as late as March 1, 1963, the date of our first liver transplantation, only 6 recipients of kidney allografts in the world had survived > one year (one in Boston [a fraternal twin] and 5 in Paris); all 6 had been treated with TBI. The longest surviving kidney recipient treated solely with azathioprine or 6-MP based therapy up to April 1962, was now 11 months postoperative (67), but we knew from contact with Murray that the patient had deteriorating renal function (blood urea nitrogen [BUN] was 110 mgm%).

## An Empirical Treatment Strategy

The experimental results in the Denver VA canine laboratory resembled those in Boston and Richmond except for a significant observation in the summer of

1962. It was shown that delayed high doses of prednisone reliably reversed the kidney (and in pilot studies liver) rejection that invariably developed under primary azathioprine therapy. Most of the dogs died from complications of steroid-induced peptic ulceration, but some lived for long periods after discontinuance of prednisone and even when azathioprine also was stopped. Using the "double drug cocktail" of azathioprine and prednisone, the Colorado clinical kidney transplant program was launched in the autumn of 1962.

The first 10 cases were compiled rapidly and reported in the October, 1963, issue of Surgery, Gynecology, and Obstetrics (9), preceding by 2 months the article in the same journal describing the first 3 clinical cases of liver transplantation (1). Four of the 10 renal recipients survived > 25 years including 2 who still bear the longest continuously functioning kidney allografts in the world after more than 38 years (Figure 1). By early 1963, the first patients in the kidney series had returned to a relatively unrestricted environment on reduced maintenance immunosuppression. We suggested that a state of relative host/graft non-reactivity had been accidentally but regularly induced by the renal allografts. The controversial, but as it turned out apposite, term "tolerance" (see later) was used to describe the change. The unprecedented good results in the kidney series triggered the liver trials.

## The Human Liver Recipients

The first 3 liver recipients were: a moribund child with biliary atresia, a 48 year old man with Laennec's cirrhosis and an unresectable hepatoma, and a 67 year old man with a completely obstructing bile duct carcinoma who previously had undergone bilateral above-knee amputations for peripheral vascular disease. Their high risk factors would preclude candidacy today. Although 2 of the recipients survived the operation, they died after 22 and 7.5 days from pulmonary emboli that were suspected to have originated from the plastic tubes used for venovenous bypasses.

## THE AFTERMATH

The Colorado kidney transplant program mushroomed overnight while the spark that had ignited it, liver transplantation, closed down world-wide following 4 more failures: 2 in Denver and one each in Boston (the Brigham) and Paris. Three advances applicable to all organs were made in Denver during the 3-1/2 year self-imposed moritorium: 1) the purification and clinical introduction in 1966 of antilymphocyte globulin (ALG) for use with azathioprine and prednisone in a triple drug regimen (17); 2) preservation techniques that allowed livers to be stored ex vivo for one to 2 days (12); and 3) the demonstration (with Paul Terasaki of UCLA) that the quality of donor/recipient HLA matching had little association with kidney transplant outcome. It was correctly assumed that tissue matching would not be crucial for the transplantation of the liver and other

extrarenal organs. When the liver program was reopened in July, 1967, during the 2-year fellowship of Carl Groth (Stockholm), multiple examples of prolonged liver recipient survival were produced (18,21).

A second liver transplant program was founded in 1968 by Roy Calne of Cambridge University and fostered by a long lasting inter-university collaboration with the hepatologist Roger Williams at King's College Hospital, London. The American and English teams sustained each other for the next dozen years, joined in 1972 by Rudolph Pichlmayr in Hannover and in 1974 by Henri Bismuth in Paris. In Denver, 170 patients underwent the operation between 1963 and 1979. Although only 56 recipients survived for 1 year, 25 were alive after 13 to 22 years at the end of 1992 (43), and 19 remain today with follow-ups of 22 to 31 years (Figure 2).

Although the feasibility of liver transplantation was now established, the results remained unacceptable (Figure 3) until the clinical introduction of cyclosporine by Sir Roy Calne whose inaugural clinical series included 2 liver recipients (28). The full potential of cyclosporine was not realized, however, until the new drug was combined with prednisone (29,30) or used in triple drug cocktails that also included azathioprine or ALG. The stampede to develop heart and other extrarenal organ transplant centers began. Nine years later, expectations moved up another notch with the substitution of tacrolimus for cyclosporine (68) (Figure 3). With tacrolimus, intestinal and pancreas transplantation became practical procedures (69,70).

## IN RETROSPECT

Most failed trials are doomed to be footnotes, if that much, in the pages of history. The 1963 article describing the first clinical attempts at liver transplantation escaped obscurity because it described on principles that were enduring. Aside from the manifold details of the difficult operation, including the role of and complications from venovenous bypass, there already was accurate insight into the importance of hepatotrophic physiology, and into the cause and treatment of metabolic acidosis. The only non-surgeon author on the 1963 report, Kurt von Kaulla, anticipated the intraoperative coagulation disorders, monitored them with serial thromboelastograms, and provided treatment with blood components and epsilon amino caproic acid (an analogue of the currently used aprotinine). Lessons from the research preceding the clinical trial had long since cross-fertilized to kidney transplantation and eventually were exploited for all kinds of allografts: core cooling by infusion of chilled intravascular fluids, in situ procurement procedures that presaged the standard flexible procedures of today, and the techniques required for close-quarter intraluminal anastomosis of blood vessels.

However, none of the generically applicable advances, or all together, remotely approached in importance the realization in the summer of 1962 that rejection

could be engineered into prolonged allograft and recipient survival by the strategic use of existing agents (i.e. azathioprine and prednisone). The cyclic pattern of convalescence and the consequent achievement of allograft acceptance remained enigmatic until it was discovered in 1992 that long-surviving organ recipients had donor leukocyte chimerism in their blood, skin, lymph nodes, and other sites as long as 3 decades after transplantation (41,43).

Then, it could be seen that the prototypic postoperative events following transplantation of all organs were the product of a double immune reaction; host-versus-graft (rejection) and graft-versus-host (Figure 4). Potentially tolerogenic "passenger leukocytes" of bone marrow origin including pluripotent stem cells had migrated from organs and engrafted peripherally. This was the seminal mechanism of organ allograft acceptance (41-46,71), an insight that enlarged the tunnel leading to the future. The epiphany ended the 35 years of speculation preceding it.

# FIGURE LEGENDS

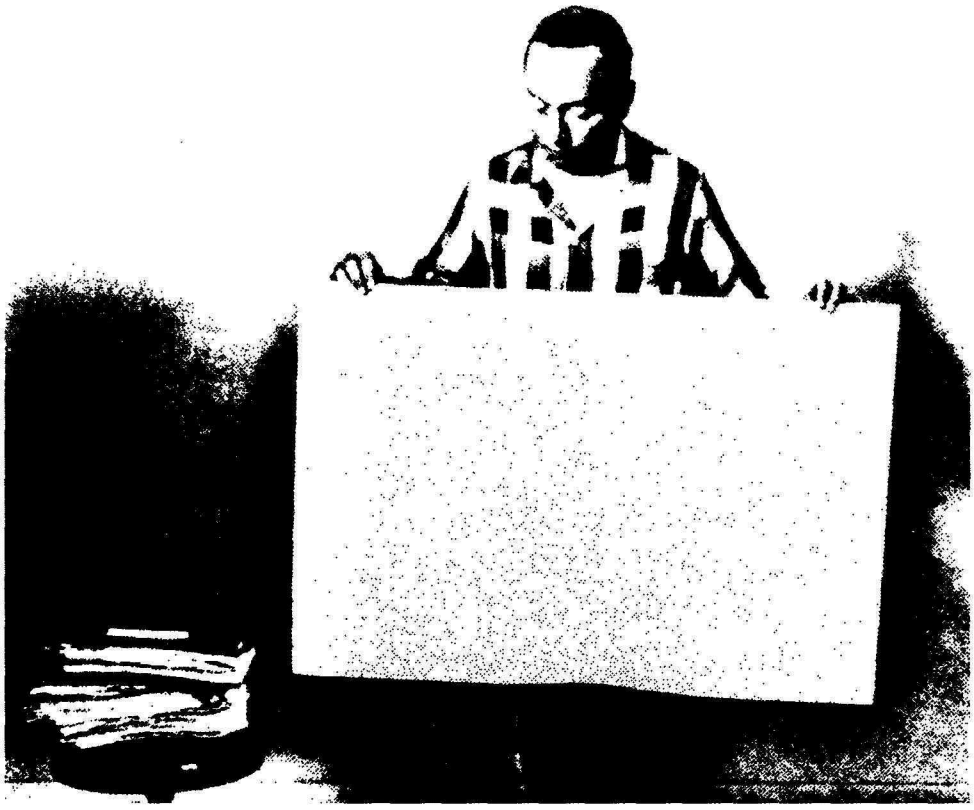

**Figure 1**
Photograph taken in 1963 of a patient who now bears the longest surviving kidney allograft in the world in his 39th post-transplant year.
The donor and recipient were of different ABO blood types (B ( A), a condition that today would preclude transplantation in most centers.

**Figure 2**
A woman (with the author) who underwent liver replacement for biliary atresia more than 31 years ago, and is the longest surviving liver recipient in the world. Her native liver contained an incidental hepatoma.

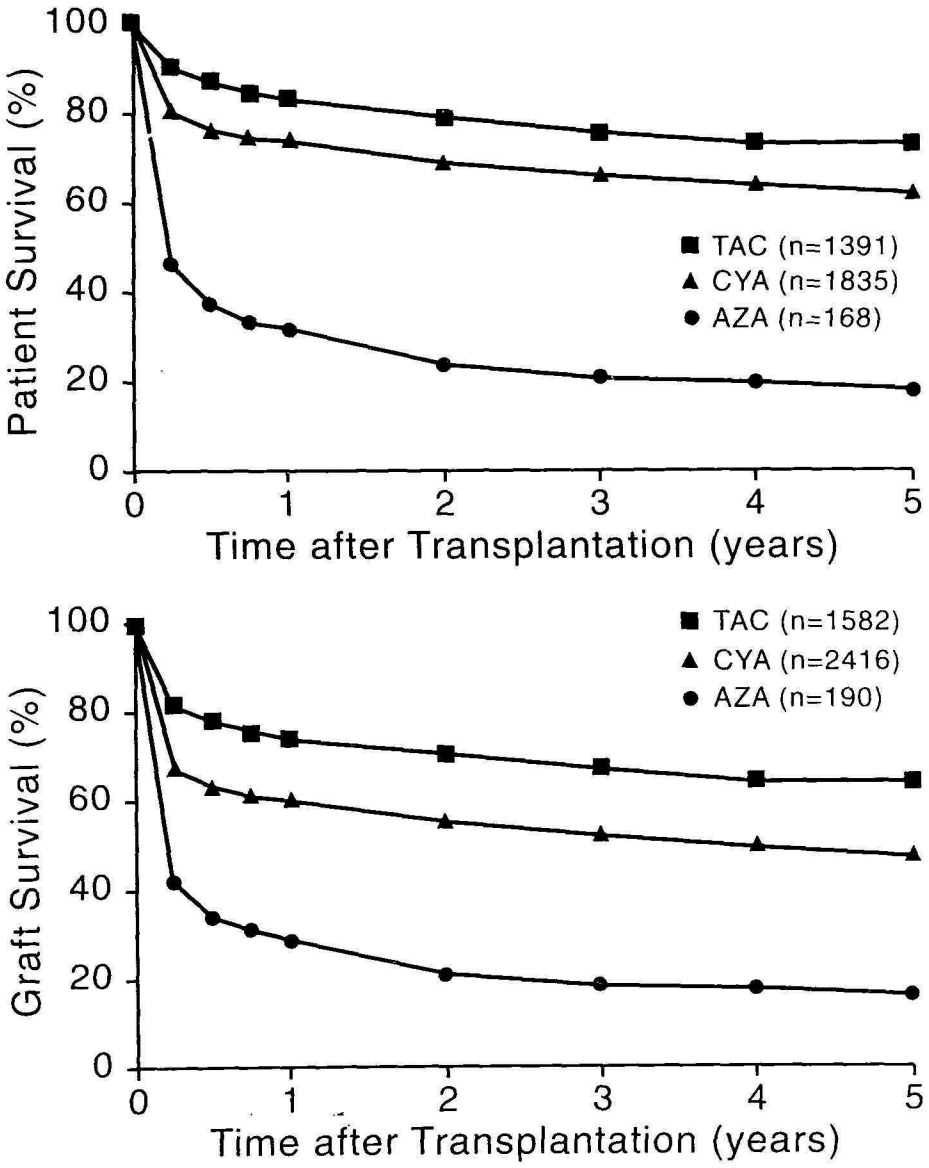


**Figure 3**

The 3 eras of orthotopic liver transplantation at the Universities of Colorado (1963-80) and Pittsburgh (1981-1993), defined by azathioprine (AZA)-, cyclosporine (CYA)-, and tacrolimus (TAC)- based immune suppression.

The same stepwise improvement was seen with kidney, heart, lung, and pancreas transplantation. Top family of curves: Patient survival. Bottom family: Graft survival. Patient survival was about 10% higher than graft survival in both the cyclosporine (1980-89) and tacrolimus eras (1989-93) because of effective retransplantation, an option that did not exist in the azathioprine era

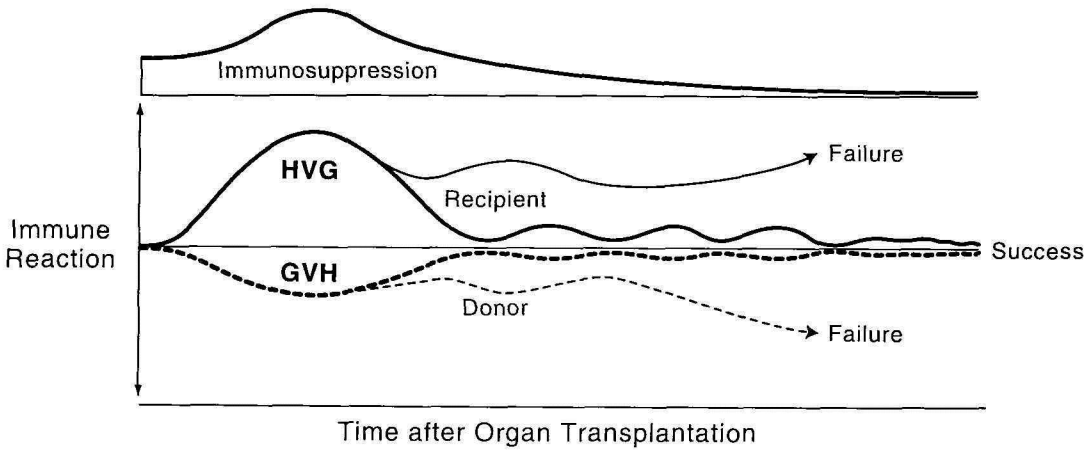


**Figure 4**
Contemporaneous host-versus-graft (HVG) and graft-versus-host (GVH) Reactions after transplantation. Treatment failure is defined as the inability to control one of the reactions, or sometimes both.
Acute reciprocal clonal exhaustion is maintained after successful transplantation by chimerism-dependent low-grade stimulation of both leukocyte populations that may wax and wane.
(By permission of the New England Journal of Medicine 339:1905-1913, 1998 [71]).

# TABLE 1: HISTORY OF LIVER TRANSPLANTATION

| AUTHOR | DESCRIPTION | YEAR 1ST PUBLISHED | REF |
|---|---|---|---|
| Welch | First mention of hepatic transplantation in the literature, with insertion of an auxiliary liver in unmodified dogs. | 1955 | 2 |
| Cannon | First article on orthotopic liver transplantation. | 1956 | 3 |
| Moore;<br>Starzl | Independent studies in Boston and Chicago of liver replacement (orthotopic transplanta-tion) in unmodified dogs. | 1960<br>1960 | 4<br>5 |
| Starzl | Transplantation in dogs of multiple abdominal viscera including liver and intestine, nearly identical to human procedures done 3 decades later. | 1960 | 6<br>7<br>8 |
| Starzl | World's first 3 attempts at orthotopic liver transplantation in humans (March 1, May 5, and June 24, 1963) with maximum survival of 21 days. | 1963 | 1 |
| Starzl | Development of the azathioprine-prednisone cocktail and recognition that kidneys were inherently tolerogenic. | 1963 | 9<br>10 |
| Marchioro<br>Brettschneider | Improvements in preservation, in situ and ex vivo. | 1963 | 11<br>12 |
| Starzl<br>Marchioro | Discovery that splanchnic venous blood of dogs contained hepatotrophic factor(s), the most important of which was later proved to be insulin; the finding dictated methods of liver allograft revascularization. | 1964 | 13<br>14 |
| Starzl | First > one year survival after liver replace-ment in any species (here mongrel dogs) with recognition of the liver's unusual ability to induce tolerance under a 3-4 month course of azathioprine, or after only a few perioperative injections of ALS or ALG (17). | 1965 | 15 |

| AUTHOR | DESCRIPTION | YEAR 1ST PUBLISHED | REF |
|---|---|---|---|
| Cordier/Garnier | Oberved that liver allografts in untreated pigs frequently were not rejected. This finding of spontaneous tolerance to livers was promptly confirmed by Peacock and Terblanche in Bristol and by Calne in Cambridge. | 1966 | 16 |
| Starzl | Clinical introduction of antilymphocyte globulin (ALG): kidneys, then livers. | 1967 | 17 |
| Starzl/Groth | First report of prolonged survival of 4 (of 7) children after orthotopic liver transplantation between July 1967 and March 1968. | 1968 | 18 |
| Calne | Report of first 4 patients in the Cambridge (England) liver replacement series. | 1968 | 19 |
| Calne | Showed that spontaneous tolerant pig liver recipients also were tolerant to skin and kidney allografts from the same donor. | 1969 | 20 |
| Starzl | Text summarizing experience at the University of Colorado with 25 liver replacements to March 1969, and 8 cases elsewhere. | 1969 | 21 |
| Starzl | Metabolic abnormality of Wilson's disease corrected, first of more than 2 dozen liver-based inborn errors cured or ameliorated with liver replacement. These liver recipients, and patients cured of mesoderm-based inborn errors by bone marrow transplantation, were the first examples of effective genetic engineering. | 1971 | 22 |
| Starzl | Principal portal hepatotrophic substance identified as insulin. | 1973 | 23<br>24 |
| Wall<br>Benichou | Improved liver preservation (5-8 hr) permitting long-distance procurement. | 1977 | 25<br>26 |
| Starzl | Systematic use of arterial and venous grafts for vascular reconstruction. | 1979 | 27 |

| AUTHOR | DESCRIPTION | YEAR 1ST PUBLISHED | REF |
|---|---|---|---|
| Calne | Cyclosporine introduced for kidneys and liver. | 1979 | 28 |
| Starzl | Cyclosporine-steroid cocktail introduced for kidneys. | 1980 | 29 |
| Starzl | Cyclosporine-steroid cocktail introduced for livers. | 1981 | 30<br>31 |
| Denmark<br>Shaw<br>Griffith | Pump-driven venovenous bypass without anticoagulation. | 1983 | 32<br>33<br>34 |
| Starzl | Standardization of multiple organ procure-ment techniques. | 1984 | 35<br>36 |
| Jamieson<br>Kalayoglu<br>Todo | University of Wisconsin (UW) solution for improved liver and other organ preservation. | 1988 | 37<br>38<br>39 |
| Starzl | FK506 (tacrolimus) – steroid immuno-suppression. | 1989 | 40 |
| Starzl | Discovery of chimerism as explanation of hepatic and other organ tolerogenicity. | 1992 | 41<br>42<br>43<br>44<br>45<br>46 |
| Starzl | Baboon to human xenotransplantation. | 1993 | 47 |

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# WINNERS OF THE 2001
# KING FAISAL INTERNATIONAL PRIZE
# FOR SCIENCE

# PROFESSOR SAJEEV O. JOHN

## Co-Winner of the 2001 King Faisal International Prize for Science

**Photo**: Professor Sajeev O. John receives his prize from
HRH Prince Abd Allah ibn Abd Al-Aziz,
The Crown Prince, Deputy Chairman of the Council of Ministers
And Head of the National Guard

# SYNOPSIS OF ACHIEVEMENTS

Professor Sajeev O. John, was born in Thiruvala, India in 1957. He received his Bachellor's degree in Physics from Massachussets Institute of Technology, and his Ph.D. in Theoretical Physics from Harvard University in Boston, Massachussets. He then held an NSERC Post-doctoral Fellowship at the University of Pennsylvania (1984-1986). He became Assistant Professor at Princeton University Department of Physics from 1986 to 1989. He also served as Consultant at Exxon Research and Engineering Laboratories (1985-89) and Bell Communications Research Laboratories (1989) and Principal Investigator, Photonics Research, Ontario. In 1989, he became Associate Professor of Physics and Member of the School of Graduate Studies at the University of Toronto. He was promoted to full Professorship in 1992. Professor John is an Associate Member of the Canadian Institute for Advanced Research and has been Project Leader of the Ontario Laser and Lightwave Center since 1991.

Professor John's current research involves three areas: light localization and photonic bands, high temperature superconductivity and multiple light scattering spectroscopy. He and his team have recently shown experimentally that a new class of dielectrics was capable of trapping light, thus providing photonic analogs of semi-conductors that could have important technological applications. They are now working on this phenomenon and the implications of light localization in quantum-electrodynamics. The group is also studying the nature and possible origins of superconductive pairing of a newly discovered magnetic field, the quantum spin liquid phase, produced by interaction of the electon spin field with the electron charge. They are also investigating the possible use of photon diffusion as a diagnostic tool for metabolic imaging in medicine, and for better understanding of the newly discovered "laser paints".

Professor John's outstanding contributions to the field of theoretical condensed matter physics has earned him several awards and fellowships.

He is currently Professor of Physics in the Department of Physics at the University of Toronto, Ontario, Canada.

Professor Sajeev John has played a major role in the discovery and elucidation of the fundamental principles of photonic band gap materials. He was the driving force behind this collaborative research, which involves the processing of information by optical means. This new technology could lead to the development of optical microchips, where light instead of electricity moves through tiny circuits. If this new technology can be reliably mass produced, it will be a major technological advance - information would be processed at the speed of light, allowing smaller and faster communication devices to be built.

# PHOTONIC BAND GAP MATERIALS: A SEMICONDUCTOR FOR LIGHT

**Sajeev John**

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## Abstract

*Light in cerlain engineered dielectric microstructures can flow in a way similar to electrical currents in semiconductor chips. These microstructures represent a new frontier in the field of optics. They provide a foundation for the development of novel micro-photonic devices and the integration of such devices into an optical microchip.*

## 1. Introduction

Electromagnetism is the fundamental mediator of all interactions in atomic physics and condensed matter physics, in other words, the force that governs the structure of ordinary matter. In a novel class of engineered dielectric materials known as photonic band gap (PBG) materials, a fundamentally new electromagnetic effect can be realized. This phenomenon is the localization of light [1,2] and it may prove central to the utilization of light waves for information and communication technologies.

In the nineteenth century , James Clerk Maxwell deduced a precise and elegant mathematical description of the propagation of light. Maxwell's theory of electromagnetic wave propagation was shortly thereafter tested and verified by Heinrich Hertz. There began the age of wireless communication. This allowed ships at sea to communicate with land. Today, the same basic discovery provides us with the use of radio, television, and mobile phones. Despite the widespread knowledge and use of Maxwell's theory of electromagnetism, it has only recently been recognized that light waves not only propagate, they can also be trapped.

The invention of the laser in the latter half of the *2Oth* century was another milestone in the science and technology of light. Laser light allows us to probe the structure of matter with unprecedented accuracy, it provides medical practitioners with a cutting tool sharper than any surgeon's knife and allows us to modulate communication signals for high speed data transfer along the internet. Today, using laser light, undersea fiber optic cables carry enormous amounts of voice communications and data with such clarity that a pin drop in Riyadh, Saudi Arabia can be heard clearly in Toronto, Canada.

Optical fibers are replacing electrical wires in shorter distance communications such as local access networks and computer to computer communications. In a completely seamless network, communications between nearby computer chips and even within a single computer chip would take place with tiny beams of laser light rather than electricity. Optical computers of this type may be faster and support neural architectures (circuit interconnections resembling that of a human brain) unlike their electronic counterparts which are restricted in architecture due to electrical cross-talk between nearby wires. That is to say, electrical current in one wire can disturb electrical signals passing through nearby wires. Laser beams, on the other hand, can co-exist without disrupting one another.

The trapping and micro-moulding of light flow needed for the applications suggested above requires materials which can scatter light much more strongly than any naturally occurring material. We experience multiple light scattering when it becomes dark on a cloudy day. Light from the sun scatters many times from water droplets, following a tortuous diffusion path before reaching the ground. The distance the light travels within the cloud before it is scattered into a random direction is called the mean free path. The effect of multiple scattering is that the amount of light transmitted through the cloud is reduced by a factor of the ratio of the cloud thickness to the mean free path. The rest comes back out the other side, which is why clouds appear white. Multiple light scattering also takes place in human tissue. Here the transport mean free path for light of one micrometer wavelength is about a millimeter .

But neither clouds nor human tissue can scatter light sufficiently strongly to localize light. For this to happen a collection of microscopic dielectric structures that scatter light a thousand times more strongly than human tissue is required. In this case the transport mean free path becomes as short as the wavelength of light itself. If, in addition to the strong resonant scattering of the individual dielectric particles, there is a periodic arrangement of the scatterers, then pathways for light propagation over specific frequency intervals can be completely removed. The removal of pathways over all directions over a band of frequencies is referred to as the creation of a photonic band gap (PBG). Dielectric microstructures that exhibit this effect are called PBG materials.

In electronic micro-circuits, electrical currents are guided by thin metal wires. Electrons are bound within the cross section of the wire by the so-called work function (confining potential) of the metal. As a result, electrical currents follow the path prescribed by the wire without escaping into the background. The situation is very different for optical waves. Although optical fibers guide light over long distances, micro-circuits of light based on fibers do not exist. This is because empty space is already an ideal conductor of light waves. The light in an optical fiber can easily escape into the background electromagnetic modes of empty space if the fiber is bent or distorted on a microscopic scale. PBG materials remove this problem by removing all the background electromagnetic modes over the relevant band of frequencies. Light paths can be created inside

a PBG material in the form of engineered waveguide channels. The PBG localizes the light and prevents it from escaping the optical micro-circuit.

## 2. Photonic Band Gap Formation

PBG materials were predicted theoretically as a means to realize the localization and trapping of light in a bulk material over a band of frequencies [3]. A direct corollary of this principle is the complete inhibition of spontaneous emission [4,5] from an atom, molecule, or electron-hole pair excitation that is placed within the PBG material. Indeed, if the emission frequency from the atom lies within the PBG, the photon that would normally be emitted forms a bound state to the atom. Nearly all of the novel consequences of PBG materials are a direct consequence of these remarkable effects. Unlike optical confinement of a single resonance mode in a high quality (Q factor) optical cavity, localized electromagnetic modes in a bulk PBG material are completely decoupled from the vacuum modes of free space. Unlike well known layered dielectric structures (including Fabry-Perot resonators and distributed feedback laser cavities) which may confine light in one spatial dimension, the PBG material facilitates coherent localization of light in all spatial directions. This unique combination of light localization and the complete control of radiative dynamics distinguishes PBG materials from any previously studied optical system.

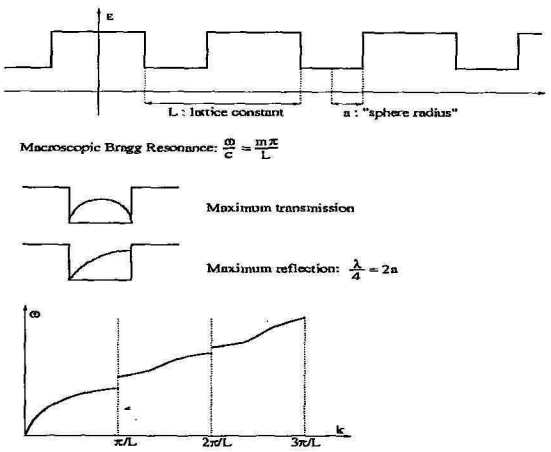


**Figure 1.** PBG formation can be regarded as the synergetic interplay between two distinct resonance scattering mechanisms. The first is the "macroscopic" Bragg resonance from a periodic array of scatterers. This leads to electromagnetic stop gaps when the wave propagates in the direction of periodic modulation when an integer number, m=1,2,3..., of half wavelengths coincides with the lattice spacing, L, of the dielectric microstructure. The second is a "microscopic" scattering resonance from a single unit cell of the material. In the illustration, this (maximum backscattering) occurs when precisely one quarter of the wavelength coincides with the diameter, 2a, of a single dielectric well of refractive index n. PBG formation is enhanced by choosing the materials parameters a, L, and n such that both the macroscopic and microscopic resonances occur at the same frequency

Photonic band gap formation can be understood as a synergetic interplay between two distinct resonance scattering mechanisms. One is the microscopic scattering resonance from the dielectric material contained in a single unit cell of the photonic crystal. A simple illustration of this is provided (Figure 1) by the scattering of a wave from a square well potential. When one half of the optical wavelength fits into the width of the well, the transmission of light from left to right is maximum and the least light is reflected. When one quarter of a wavelength fits into the width of the well, the least amount of light is transmitted and the maximum amount of light is reflected. This quarter wavelength condition is a simple example of the condition for a microscopic scattering resonance. The second resonance is macroscopic resonance from the geometrical arrangement of the repeating unit cells of the dielectric microstructure. If there is a periodic arrangement of unit cells, this is called Bragg scattering. This occurs whenever the spacing between adjacent unit cells is an integer multiple of half of the optical wavelength. Photonic band gap formation is facilitated if the geometrical parameters of the photonic crystal are chosen so that both the microscopic and macroscopic resonances occur at precisely the same wavelength. In addition, both of these scattering mechanisms must individually be quite strong. In practice, this means that the underlying solid material must have a very high refractive index (typically about 3.0 or higher) while at the same time exhibit negligible absorption or extinction of the light (less than I decibel of attenuation over a centimeter). These conditions on the scattering strength, the geometry, and the purity the dielectric material severely restrict the set of engineered dielectrics that exhibit a PBG. Candidate materials for the PBG backbone include silicon, germanium, gallium arsenide, and indium phosphide.

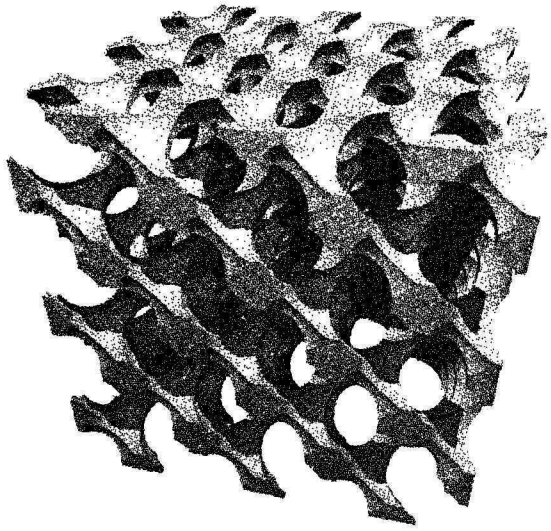

**Figure 2.** The "inverted diamond" structure was one of the first prototype structures predicted to exhibit a large and robust 3D PBG. It consists of an overlapping array of air spheres arranged in a diamond lattice. This structure can be mimicked by drilling an array of criss-crossing cylindrical holes into a bulk dielectric. The solid backbone consists of a high refractive index material such as silicon leading to a 3D PBG as large as 27% of the center frequency. The minimum refractive index (of the backbone) for the emergence of a PBG is roughly 2.0. Practical difficulties in the synthesis of this structure have motivated simpler but closely related designs such as the "woodpile" structure (see **Figure 9**).

Scalar waves (sound waves and other compression waves in solids) readily exhibit complete three-dimensional gaps for simple structures such as a face-centered cubic (FCC) lattice of spherical scatterers [6]. In contrast, electromagnetic waves involve three component electric and magnetic field vectors. This leads to much more restrictive conditions on the dielectric constant, the solid volume fraction, and the microstructure connectivity for the formation of a PBG. One very widely studied class of PEG materials is that based on a diamond lattice of dielectric scatterers. For example, a diamond lattice of very high dielectric constant, nonoverlapping spheres exhibits a PBG for which electromagnetic wave propagation is completely forbidden over a narrow frequency band [7]. An "inverse diamond" lattice of overlapping air spheres in a high refractive index background (**Figure 2**) exhibits a much larger PEG. In the microwave regime, other diamond-like structures obtained by drilling cylindrical holes in a bulk dielectric material (with refractive index of 3.5) have been demonstrated to exhibit band-gap to center frequency ratios as large as 20% [8]. Since then, numerous structures amenable to layer by layer fabrication have been suggested, the most notable being the "woodpile" structure [9,10,11,12]. A number of structures have already been fabricated with PBG's in the range of millimeter waves [13,14,15]. The diamond structure and its cousins constitute a family of PBG materials which are characterized by a large and

complete PBG between the second and third bands (fundamental gap) in the photonic band structure. The FCC lattice structure, on the other hand, does not exhibit a complete PBG between the 2nd and 3rd bands. Instead it has a small PBG between the 8th and 9th bands. While it has been a common belief that only the diamond structure is associated with large and complete PBG's, very recently a new class of microstructure based on a tetragonal lattice has been discovered that exhibits a large PBG between the 4th and 5th electromagnetic dispersion bands [O. Toader and S. John to be published]. An illustration of such a lattice consisting of square spiral posts is shown in **Figure 3**. When the posts are made of silicon, this structure exhibits a 15%PBG. The corresponding electromagnetic density of states is shown in **Figure 4**. This structure is amenable to micro-fabrication using a technique called Glancing Angle Deposition (GLAD) [16,17].

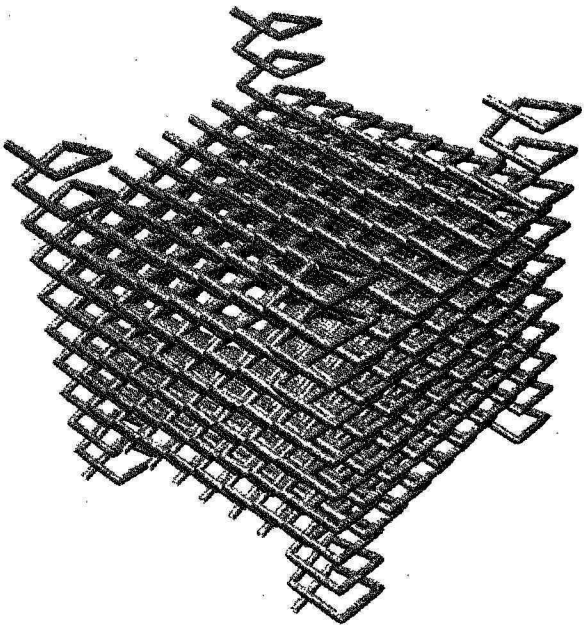

**Figure 3.** The Tetragonal lattice of Square Spiral posts exhibits a complete 3D PBG and can be synthesized using a glancing angle deposition (GLAD) method. This chiral structure consists on slightly overlapping square spiral posts grown on a 2D substrate that is initially seeded with a square lattice of growth centers. Computer controlled motion of the substrate leads to spiraling growth of the posts. A large and robust 3D PBG emerges between the 4th and 5th bands of the photon dispersion. The "inverse structure" consisting of air posts in a solid background exhibits an even larger 3D PBG.

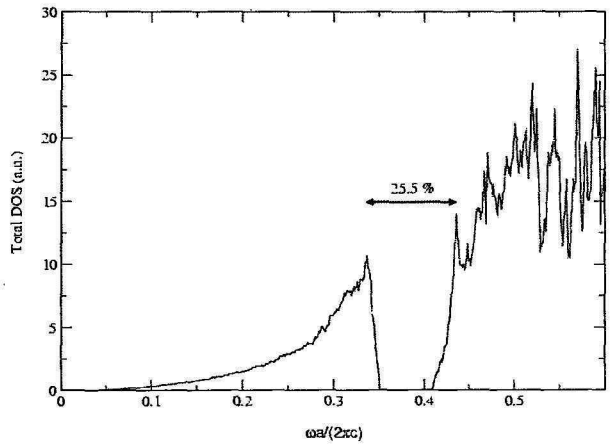


**Figure 4.** Electromagnetic density of states as a function of frequency for the tetragonal square spiral structure of **Figure 3.** The total 3D density of states (DOS) vanishes over an interval of 15% of the center frequency between the 4th and 5th photon dispersion bands. In this interval, the material is "emptier than vacuum" in the sense that even the zero point (quantum) fluctuations of the electromagnetic field have been eliminated. The size of the (larger) pseudogap over which the DOS differs significantly from that of ordinary vacuum is roughly 25% of the center frequency.

Simple applications of PBG materials can be found in the microwave to millimeter wave range. For instance, an antenna mounted on a conventional dielectric substrate emits the majority of its radiation into the substrate itself. If the substrate is engineered into the form of a PBG material with a gap at the radiation frequency, the losses can be minimized, leading to highly directional transmitters [18,19]. Other applications include optical filters with tailor made characteristics [20] and cladding material for preventing losses in waveguide structures that contain bends or junctions [21,22,23]. Nevertheless, it is for visible and near-infrared frequencies where PBG materials are likely to have their most important impact. For example, applications in telecommunications require the fabrication of PBG materials with a gap centered in the 1.3-1.5 μm range, where there is minimal absorption of light in silica based optical fibers. These applications include the design of ultra-compact lasers that emit coherent light with almost no pumping threshold, all-optical switching fabrics for routing data along the internet, optical switches with an on-off cycle time of less than a trillionth of a second, and all-optical transistors.

PBG materials also represent a new frontier in fundamental aspects of quantum and nonlinear optics. While linear wave propagation is absent in the gap of a PBG material, nonlinear propagation effects can still occur [24,25,26]. When the backbone of the PBG exhibits a nonlinear refractive index (that depends on the intensity of the electromagnetic wave field) certain high intensity "light bullets"

(solitary waves) can pass through the material even at frequencies within the gap. In addition, PBG materials exhibit novel quantum optical features, related to the drastic alteration of the photon density of states (DOS). A vanishing DOS leads to bound photon-atom states, [27,28] suppressed spontaneous emission [4,5,29,30] and strong localization of photons [3,27,28,31]. Localization of photons implies that emission of light from an initially excited atom occurs in a way that is very different from that in ordinary vacuum. In a PBG material, the atom has a long time memory of the fact that it was optically excited at an earlier time. One consequence of such memory and intrinsic feedback is that lasing can occur at a photonic band edge without recourse to a standard laser cavity involving a pair of mirrors. Other novel phenomena predicted to occur in a PBG material include: (i) collective switching of two-level atoms from ground to excited state with low intensity applied laser fields leading to all-optical transistor action [32], (ii) single atom memory effects for possible quantum computer applications [33], and (iii) low threshold and other anomalous nonlinear optical response [34].

## 3. Two-Dimensional PBG materials

In many applications, the polarization state of guided light can be fixed in a particular direction and only the passive optical guiding characteristics of a PBG material come into play. Two-dimensional (2D) periodic microstructures are often sufficient for such applications. For 2D periodic dielectrics, advanced planar micro structuring techniques borrowed from semiconductor technology can greatly simplify the fabrication process. Such structures are referred to as photonic crystals exhibiting a 2D PBG or 2D PBG materials. The "aspect ratio" of a 2D PBG material is defined as the ratio of the sample depth (vertical direction) to the lattice constant (transverse direction).

High-quality photonic crystals with aspect ratios of up to 5:1 can be manufactured through plasma etching or electron beam lithography techniques [35,36,37]. These are sometimes referred to as membrane structures. Alternatively, high aspect ratio 2D PBG structures can be manufactured by photo- electrochemically growing ordered macropores into a silicon wafer [38,39]. With these 2D PBG materials aspect ratios of 200: 1 and 2D band gaps centered at wavelengths in the 1.3-1.5μm have been achieved [40].

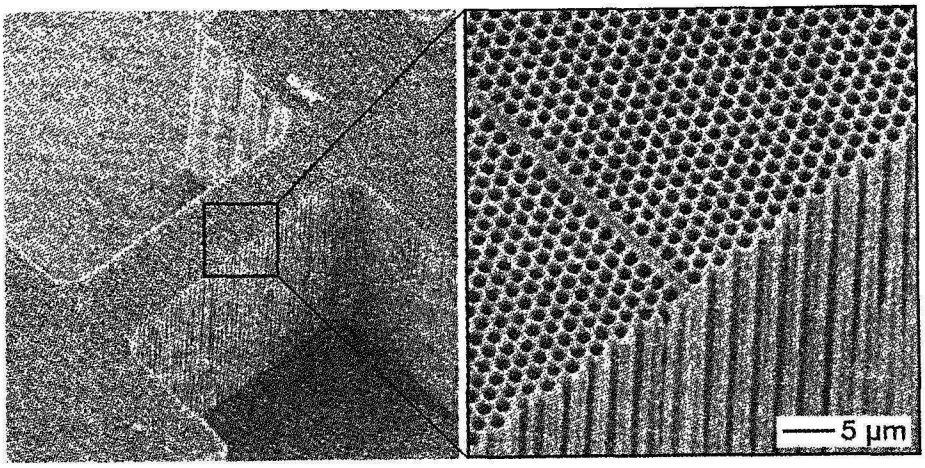


**Figure 5.** Laterally structured sample of macro-porous silicon material with an incorporated defect line. The H-like structure facilitates the positioning of a fiber for the coupling in and out of light. The lattice constant is 1.5 µm and the pore height is 100 µm. For a suitably focused beam, the structure represents a truly 2-0 PBG material with a band gap around 3 µm. (courtesy of Ulrich Gosele, Max-Planck Institute for Microstructure Physics, Halle, Germany).

The quality of 2D PBG materials synthesized using the photo-electrochemical process is shown in **Figure 5**. Here, we depict a bar of macroporous silicon consisting of 22 pore layers with a lattice constant of 1.5 J.lm. This structure exhibits a 2D PBG centered near 3 J.lm. That is to say there is a band of frequencies over which light polarized with either the electric field (E-polarization) or magnetic field (H-polarization) parallel to the pores cannot propagate through the material. During the fabrication process of a 2D PBG material, light paths within the gap can be engineered through the introduction of defects. For instance, if a single pore is modified or left out altogether (by placing an etch mask over silicon wafer), an optical microcavity is formed and leads to a localized mode of light inside the PBG. A chain of such point defects can act as a linear waveguide channel [23,41] and facilitate very sharp wave guide bends. It can also provide ultra-small beam- splitters, Mach-lehnder interferometers, and functional micro-optical elements such as wavelength add-drop filters [42]. Some defecf structures [43] are shown in **Figure 6**.

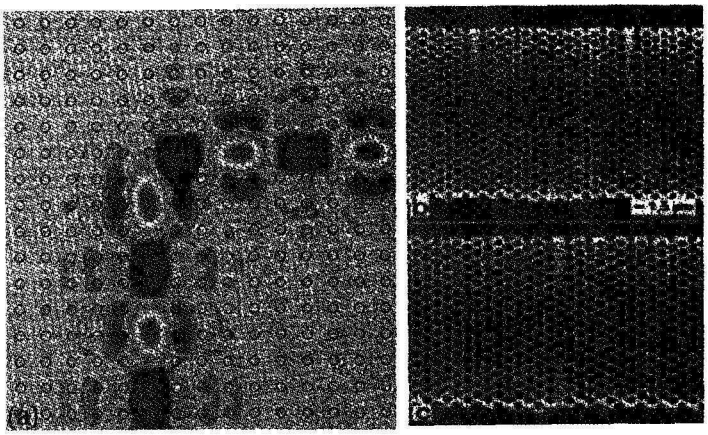

**Figure 6.** (a) Sharp bend waveguide channel in a 20 photonic crystal. The colors show the propagation of a electromagnetic mode around the bend with no reflection or scattering losses (courtesy of J.O.Joannopoulos, Massachusetts Institute of Technology). (b,c) Electron micrographs of other defect structures realized in macroporous silicon with a lattice constant of 1.5 ~m. The split waveguide in (b) may be used as an optical interferometer and the air holes within the waveguide channel (c) can be used as Bragg mirrors to isolate a resonator cavity within the waveguide. (courtesy of Max-Planck Institute for Microstructure Physics, Halle, Germany).

## 4. Two-Dimensional Photonic Crystal Devices

An add-drop filter for a wavelength division multiplexed (WDM) communication system is depicted in **Figure 7**. Here, light from an optical fiber carrying many different frequencies, Fl, F2,... is inserted into a 2D PBG structure by means of a wave guide channel (missing row of holes). The frequencies Fl, F2,... lie within the 2D PBG and cannot escape from the waveguide channel except in places where the periodicity of the background pores is disrupted by means of defects. For example, a hole that is larger than all the other background holes can act as a resonator which picks of a particular frequency, say Fl, from the wave guide channel, while allowing other frequencies to propagate freely along the wave guide. Channel drop tunneling through localized defect modes with more sophisticated geometries have already been designed [42] and tested [44]. A collection of such defects could serve to pick up a band of frequencies and route them to a specified destination.

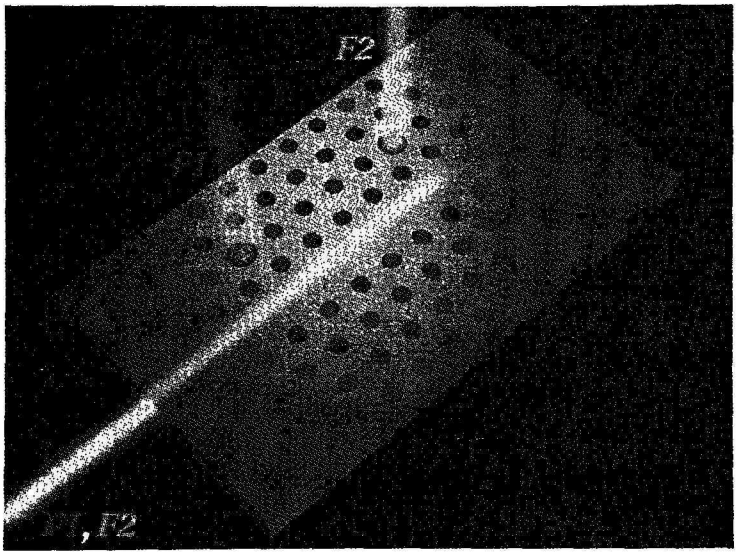


**Figure 7.** Add-drop filter for a dense wavelength division multiplexed optical communication system. Multiple streams of data carried at different frequencies F1, F2, etc. (yellow) enter the optical micro-chip from an external optical fiber and are carried through a wave guide channel (missing row of pores). Data streams at frequency F1 (red) and F2 (green) tunnel into localized defect modes and are routed to different destinations. The frequency of the drop filter is defined by the defect pore diameter which is different from the pore diameter of the background photonic crystal.

A number of prototype "active" devices based on 2D PBG hetero-structures have been designed and tested. For example 2D photonic crystal micro-lasers already rival the best available micro-cavity lasers both in size and performance. For a 2D PBG the localization of light and control of spontaneous emission from excited two-level systems is incomplete. Nevertheless, low threshold lasing from ultra-compact devices has been demonstrated [35,45].

**Figure 8** depicts two distinct types of micro-lasers. The first (shown in **Figure 8a**) is a "band edge micro-laser" in which light emission from electrically injected electron-hole pairs in a multiple quantum well array occurs near the band edge of a 2D PBG. It has been predicted [29] that strong feedback and memory effects accompany collective light emission near the photonic band edge. Near a true 3D photonic band edge, this would lead to lasing without a conventional optical cavity [31]. A precursor to this effect is seen in the 2D band edge micro-laser in which lasing occurs preferentially at the 2D photonic band edge [45] even though the emission from the active region has a broad frequency distribution.

The second type of micro-laser (shown in **Figure 8b)** utilizes a localized state defect mode as a laser cavity [35]. Here, the localized electromagnetic mode is associated with a missing hole in the 2D triangular lattice. This particular structure has been proposed as the "world's smallest micro-laser" with a cavity volume of 0.03 cubic microns. Spontaneous emission from electron-hole pair recombination in the multiple quantum well active region occurs preferentially into the localized state. Since the photonic crystal is two-dimensional, spontaneous emission is not exclusive to the lasing mode. This results in a finite pumping threshold before lasing occurs.

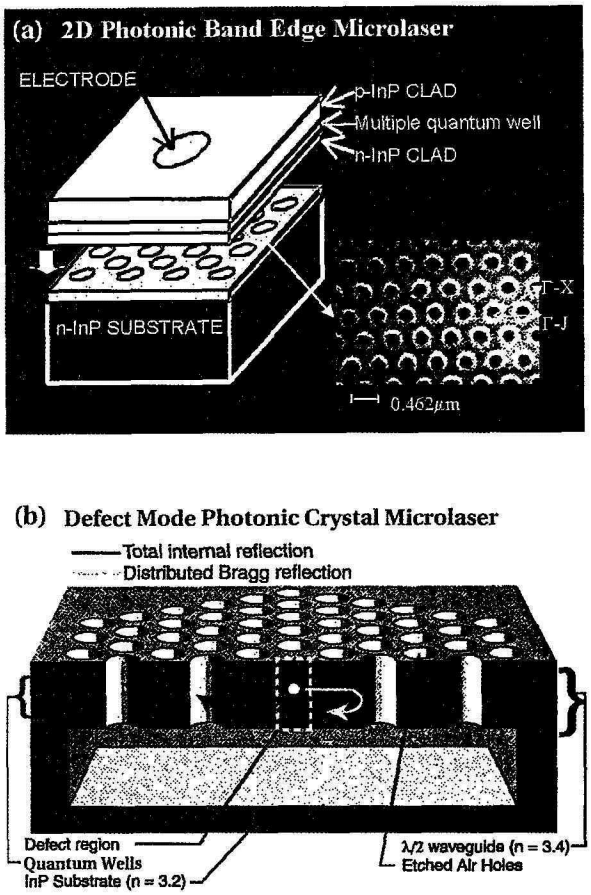


**Figure 8.** Architectures for 2D photonic crystal micro-lasers. **(a)** The Band Edge micro-laser utilizes the unique feedback and memory effects associated with a photonic band edge and stimulated emission (arising from electron-hole recombination) from the multiple quantum well active region occurs preferentially at the band edge. There is no defect mode engineered in the 2D PBG (courtesy of S. Noda, Kyoto University). **(b)** Defect Mode micro-laser requires the engineering of a localized state of light within the 2D PBG. This is created through a missing pore in the 2D photonic crystal. Stimulated emission from the multiple quantum well active region occurs preferentially into the localized mode. (courtesy of Axel Scherer, California Institute of Technology).

## 5. Synthesis of Three-dimensional PBG materials

While 2D PBG materials can confine light in two spatial dimensions, 3D PBG materials facilitate complete localization of light and can facilitate complete inhibition of spontaneous emission of light from atoms, molecules, and other excitations. If the transition frequency from such an atom lies within a 3D PBG, the photon that would normally be emitted and escape from the atom forms a bound state to the atom. Such feedback effects have important consequences on laser action from a collection of atoms. Indeed lasing may occur near a photonic band edge even without the need for mirrors as in a conventional laser cavity.

### 5.1 Layer-by-layer structures

The "woodpile" structure [9,10] represents a three-dimensional PBG material that lends itself to layer-by-layer fabrication. It resembles (see **Figure**) a criss-crossed stack of wooden logs, where in each layer the logs are in parallel orientation to each other. To fabricate one layer of the stack, a $SiO_2$- layer is grown on a substrate wafer, then patterned and etched. Next, the resulting trenches are filled with a high-index material such as silicon or GaAs and the surface of the wafer is polished in order to allow the next $SiO_2$ layer to be grown. The logs of second nearest layers are displaced midway between the logs of the original layer. As a consequence, 4 layers are necessary to obtain one unit cell in the stacking direction. In a final step, the $SiO_2$ is removed through a selective etching process leaving behind the high-index logs. To date [46], [47], this type of complex micro-lithography has lead to the successful fabrication of an 8 layer structure (2 unit cells) in the stacking direction.

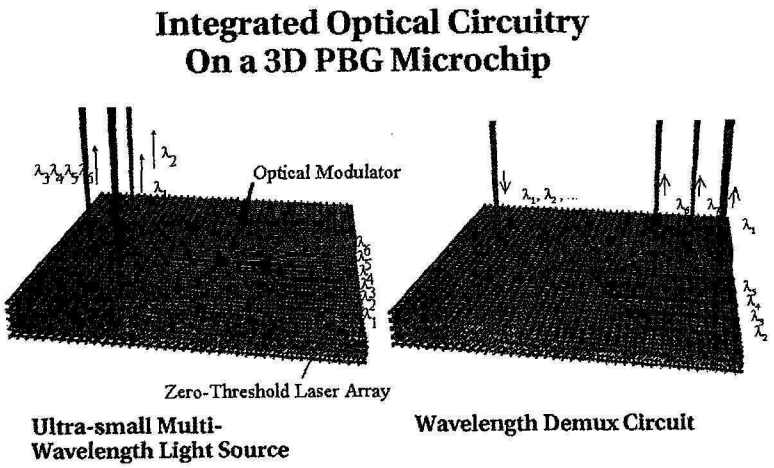


**Figure 9.** *An artist's conception of a 3D PBG woodpile structure into which a micro-laser array* and de-multiplexing (DEMUX) circuit have been integrated. (courtesy of S. Noda, Kyoto *University, Japan).*

## 5.2 Self-organizing structures

In three dimensions a number of large-scale self-assembling periodic structures already exist. These include colloidal systems [48,49] and artificial opals [50,51]. Unfortunately, these readily available materials do not satisfy the necessary criteria of high index contrast and correct network topology to produce a complete PBG. Theoretical studies, however, indicate the possibility of a complete PBG in closely related structures. Face centered cubic lattices consisting of low dielectric inclusions in a connected high dielectric network (henceforth called inverse structures) [52] can exhibit small PBGs. The recipe of producing inverse structures from artificial opals is to infiltrate them with a high dielectric material such as silicon [53] and to subsequently etch out the $SiO_2$ spheres, leaving behind a connected network of high dielectric material with filling ratios of about 26% by volume. Such a "Swiss cheese structures" with air voids in a silicon backbone is displayed in **Figure 10**. This large-scale inverse opal PBG material exhibits a complete 5% PBG relative to its center frequency at 1.5μm [53].

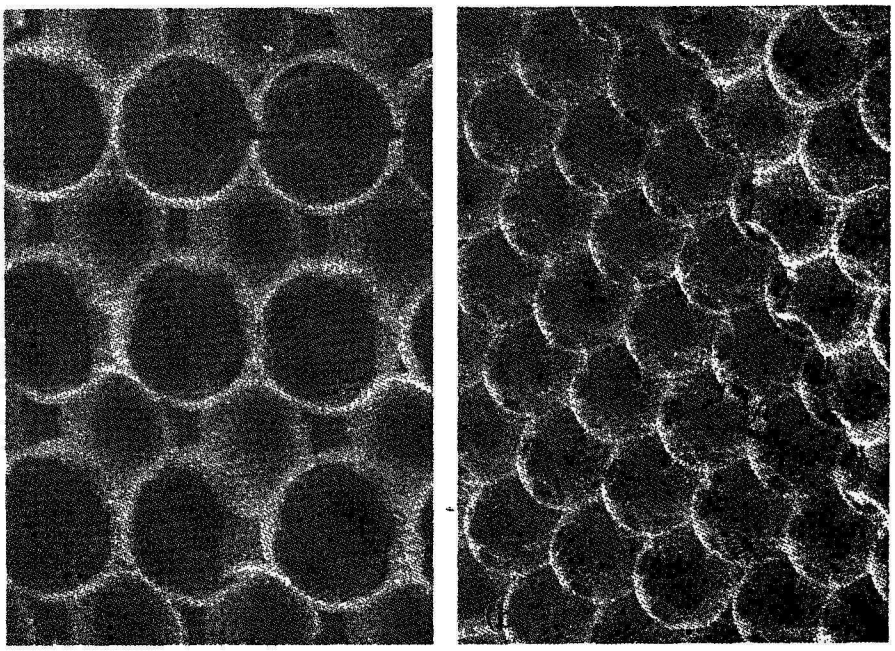

**Figure 10.** Scanning Electron Microscope (SEM) pictures of cross section along **(a)** the cubic (110)- direction and **(b)** the cubic (111)-direction of a silicon inverse opal with a complete 5% PBG around 1.5 μm. The structure has been obtained through an infiltration of an artificial opal with silicon (light shaded regions) and subsequent removal of the $SiO_2$ spheres of the opal. The air sphere diameter is 870 nanometers. Clearly visible is the incomplete infiltration (diamond shaped voids between spheres) and the effect of sintering the artificial opal prior to infiltration (small holes connecting adjacent spheres).

## 6. Quantum and Nonlinear Optics in 3D PBG Materials

Photonic band gap materials represent a fundamentally new paradigm for low threshold nonlinear optical phenomena. The PBG affects the light-matter interaction in a fundamental way. For instance, if the transition frequency of an excited atom embedded in such a material lies within the complete PBG, spontaneous emission may be completely suppressed and a bound photon-atom state is formed instead [27,28]. Based on these principles numerous applications for active devices have been suggested. Two illustrative examples are given below.

### 6.1 Low Threshold Resonant Nonlinear Optics

The ability to achieve ultrafast nonlinear optical response in a non-absorbing material is crucial in applications such as all-optical switches and other nonlinear devices for integrated optical circuits. In a conventional Fabry-Perot device containing a weakly nonlinear layer, transistor-like response requires relatively high intensity laser fields. The situation may be dramatically different in the context of a three-dimensional PBG material where the inhibition of spontaneous emission from atoms and molecules is essentially complete.

Consider the injection of a classical monochromatic electromagnetic wave of frequency $\omega$ into a 3D PBG material by means of a single mode wave guide channel. Suppose this wave guide channel contains a small active region of optically excitable two-level systems (confined electron-hole pair excitations or atoms) with a radiative transition at frequency $\omega_0$ such that the detuning $? = \omega$ □ $\omega_0$ □ $\omega_0$. For weak fields, the response of the two-level atom is that of a simple harmonic oscillator since the atom spends the majority of time in its ground state. Whenever the external field excites the atom, it quickly returns to its ground state due to the rapid rate of spontaneous emission. As the external field intensity is increased, the upper state population increases and eventually saturates. This is associated with nonlinear response. The appropriate mechanical analogy for the quantum two-level system is no longer a classical harmonic oscillator, but rather a simple pendulum (atomic Bloch vector) whose coordinates are given by the different components of the 2X2 atomic density matrix. Small angle oscillation of the atomic Bloch vector describes linear response whereas large angle oscillations probe the nonlinear susceptibility of the atom. The threshold external laser intensity required to probe nonlinear response is directly proportional to the rate of spontaneous emission [54].

This widely accepted picture of nonlinear optical response in ordinary materials is no longer applicable in a three-dimensional PBG material in which two-level atoms have a radiative transition at frequency $\omega_0$ that lies within the PBG. Inside a PBG, the rate of spontaneous emission (and accordingly the threshold intensity for nonlinear response) formally vanish. While this is suggestive of low threshold nonlinear optical response, it is in fact an indication that the entire

derivation of the optical susceptibility must be carefully re-examined in the context of the PBG. In particular, the conventional textbook susceptibility is based on retaining only the leading order photon-atom interaction, namely spontaneous emission. In the PBG, this leading process is almost absent. Therefore, it is necessary to consider the next process, namely resonance dipole-dipole interaction (RDDI) between a pair of two-level atoms. A straightforward derivation [34] of the nonlinear susceptibility in this context leads to some remarkable effects. For example, it is possible (at relatively low field intensities) to completely saturate the imaginary (absorptive) part of the susceptibility while retaining a large real part. This arises in a situation where a collection of atoms inside a PBG interact randomly by RDDI and an external field enters the material through a small number of defect (wave guide) modes. Due to the inhibition of spontaneous emission, the single atom absorptive transition is saturated at nearly the one-photon level. However, due to the random nature of RDDI, the induced atomic dipoles are randomly oriented and remain highly susceptible to alignment (macroscopic polarization) by the external field.

### 6.2 Collective Switching and Transistor Effects

A second illustration of novel radiation-matter interaction in a PBG material arises if a collection of two-level atoms is selected such that their radiative transition lies very close to a photonic band edge. Near the photonic band edge, the electromagnetic density of states varies rapidly with frequency and the spontaneous emission processes cannot be adequately described using Fermi's Golden Rule. We refer to the case in which the density of states exhibits singularities or abrupt variation as a "colored vacuum". In the colored vacuum of a photonic band edge it is possible to achieve population inversion for a collection of two-level atoms driven by a weak coherent pump laser field. As the number of atoms in a cubic wavelength increases, this switching from a passive medium (most atoms in ground state) to an active medium (population inverted) occurs sharply as the external pump laser intensity is increased. In the region of this collective jump in atomic population, there is a large differential optical gain. If the pump laser intensity is chosen slightly below threshold for population inversion, a second control laser field can be introduced to act as a gate which determines whether the pump laser field is either attenuated or amplified by the medium (see **Figure 11**). Since all of these processes involve coherent radiation-atom interactions, this system may form the basis of a low threshold optical switch or all-optical transistor [32].

When a coherent laser field with average incident energy density $W$ and frequency $\omega$ interacts with a collection of $N$ two-level atoms in ordinary vacuum, the steady state behavior of the system is governed by the well-known Einstein rate equations. These equations implicitly make use of the smooth nature of the vacuum density of states $N(\omega)=\omega^2/(\pi^2c^2)$ in the vicinity of the atomic transition frequency $\omega$ ? $\omega_0$. In steady state equilibrium, the ratio of the number of excited

atoms, $N_2$, to the total number of atoms N increases with W but always remains below 1/2 [55]. In other words, it is not possible to invert a collection of two-level atoms with a coherent laser field.

From a more quantum mechanical point of view, the external laser field may be regarded as consisting of a large collection of *n* photons. The atom-radiation field interaction breaks the degeneracy between a state consisting of a given atom in its excited state and (*n*-1) photons in the radiation field and a state consisting of the given atom in its ground state and *n*-photons in the radiation. The true quantum mechanical states of the system are called dressed atomic states (linear combinations of the two degenerate possibilities). The energies of the dressed states are shifted from their bare values by an $?\sim\mu_{ba}|E/h$ (Rabi frequency) where $\mu_{ba}$ is the atomic dipole matrix element and |E| is the laser field amplitude. This leads to the well-known Mollow fluorescence spectrum in ordinary vacuum [55]. Rather than a single peak in the atomic spectrum centered at the bare atomic transition frequency $\omega_0$, the fluorescence spectrum exhibits three peaks centered at $\omega_0$, $\omega_0 + ?$, and $\omega_0 - ?$.

The Einstein rate equation picture of the steady state atomic inversion relies on the fact that the vacuum density of electromagnetic modes $N(\omega)$ is relatively smooth on the scale of $\Delta$. That is to say, the Einstein picture assumes that the rate of spontaneous emission in the Mollow sidebands at $\omega_0+?$ and $\omega_0-?$ is roughly the same. In ordinary vacuum $(N(\omega) = \omega^2/(\pi^2 c^3))$ this assumption is easily satisfied. Moreover, in ordinary vacuum, very high intensity fields are required to observe any Mollow splitting whatsoever. The situation is dramatically different in a PBG material where the density of states itself exhibits rapid variation from frequency $\omega_0 - ?$ to $\omega_0 + ?$. Another striking property of the photonic band edge is that atomic line splitting may be achieved with very low intensity fields. In particular, vacuum Rabi splitting of an atomic transition placed directly at the band edge has been predicted [27,28,29]. In other words, at a band edge, significant splitting can be expected in an atomic line even in the presence of a single photon! This leads to a dramatic modification of the Einstein picture.

In a weak applied laser field, atoms with a bare transition frequency $\omega_0$ which coincides with a photonic band edge will exhibit a pair of dressed states that straddle the band edge [27,28,29]. These two spectral sidebands will experience vastly different rates of spontaneous emission. The spectral component that is pulled into the gap will exhibit negligible decay. This component corresponds to a photon-atom bound state [27]. The spectral component that is pushed away from the gap can exhibit emission into the allowed modes of the photonic band. Population inversion for a collection of such atoms can readily be achieved by an external laser field due to trapping of excitation energy in the photon-atom bound state component [32].

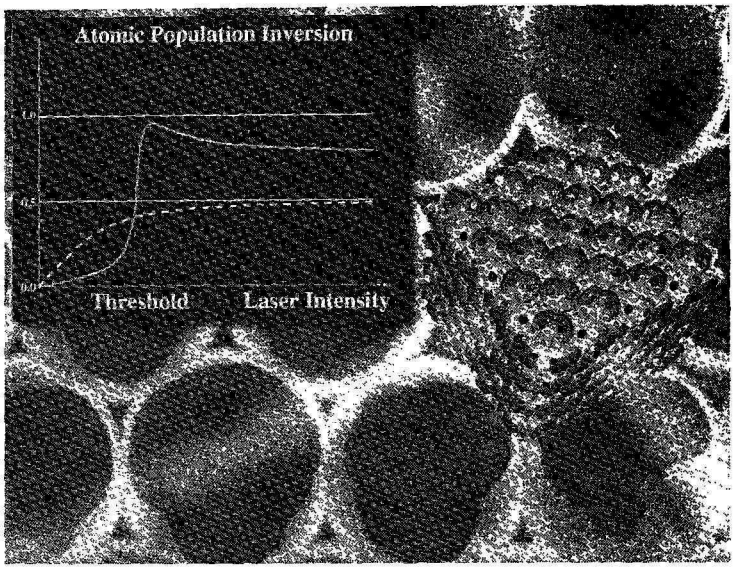


**Figure 11.** Micro-photonic all-optical transistor may consist of an active region buried in the intersection of two wave-guide channels in a 3D PBG material. The two-level systems ("atoms") in the active region are coherently pumped and controlled by laser beams passing through the wave guides. In addition, the 3D PBG material is chosen to exhibit an abrupt variation in the photon density of states near the transition frequency of the atoms. This leads to atomic "population inversion" through coherent pumping, an effect which is forbidden in ordinary vacuum. The inversion threshold is characterized by a narrow region of large differential optical gain (solid curve in the inset). A second, "control laser" allows the device to pass through this threshold region leading to strong amplification of the output signal. In ordinary vacuum, population inversion is unattainable (dashed curve in the inset).

The resulting collective switch in atomic population as a function of applied field intensity is depicted schematically within the inset of **Figure 11.** Details of this result may be found in reference 32]. This transition becomes increasingly sharp as the number of atoms increases and defines a region of large differential optical gain. It is expected that the collective switch can be achieved for a very low applied field and that the switching effect is robust with respect to variety of dephasing effects due to lattice vibrations in the host PBG material.

## 7. Tunable PBG materials

For many applications it is advantageous to obtain some degree of tunability of the photonic band structure through electro-optic effects. This may be useful in routing of signals through an optical communication network and provide flexibility to reconfigure the routing as conditions in the network change. One of the great advantages of PBG materials is that by volume, most of the material consists of pores. These pores can be infiltrated with other electro-optically

active materials which enable reconfiguration of the underlying photonic band structure either globally or locally. Tunability may be obtained by controlling one or several forms of optical anisotropy of the constituent materials. For example the science of liquid crystals has spawned an entire industry related to these electro-optic effects. Inverse opal structures provide a highly efficient scattering system as illustrated by the complete PBG of silicon inverse opals (**Figure 10** and **Figure 11**). The nearly 75% empty volume of this structure is ideally suited for infiltration by a low refractive index liquid crystal with strong optical anisotropy making them efficacious for electro-optic tuning effects. In particular, a change in the orientation of the nematic director field with respect to the inverse opal backbone by an external electric field can completely open or close the full, three-dimensional PBG [56]. The resulting tunability of spontaneous emission, waveguiding effects, and light localization may considerably enhance the technological value of a composite liquid crystal PBG material over and above that of either a bulk liquid crystal or a conventional PBG material by itself. A tunable optical microchip which routes light from a set of optical fibers is shown in **Figure 12**.

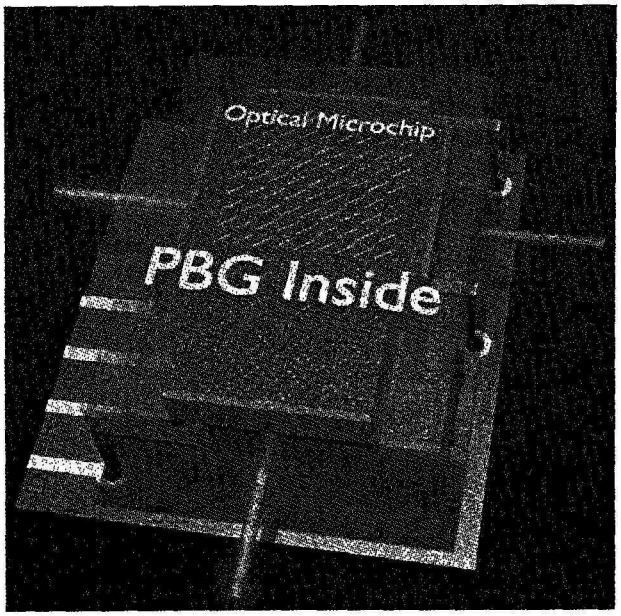


*Figure 12. Artist's depiction of an electro-actively tunable PBG routing device. Here the PBG material has been infiltrated with an optically anisotropic material (such as a liquid crystal) exhibiting a large electro-optic response. When a voltage is applied to the electro-optically tunable PBG, the polarization state (yellow arrows) can be rotated, leading to corresponding shifts in the photonic band structure. This allows light from an optical fiber to be routed into one of several output fibers.*

## 8. Outlook

The synergetic interplay between advanced material science, theoretical analysis and modern spectroscopy has been and continues to be the driving force for the field of PBG materials. Recent advances in micro-structuring technology have allowed the realization and controlled engineering of three-dimensional PBG structures at the near IR as well as the visible frequency spectrum of electromagnetic radiation. In a parallel development, the theoretical description of PBG materials has matured to the point where it provides a reliable interpretative as well as predictive tool to both material synthesis and spectroscopic analysis of these novel semiconductors for light. The current state of PBG research suggests that this field is at a stage comparable to the earJy years of semiconductor technology shortly before the invention of the solid state electronic transistor by W. Shockley, J. Bardeen, and W .H. Brattain. If this analogy continues to hold, one may find the PBG materials at the heart of a $21^{st}$ century revolution in optical information technology similar to the revolution in electronics we have witnessed over the latter half of the $20^{th}$ century.

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# PROFESSOR CHEN NING YANG

## Co-Winner of the 2001 King Faisal International Prize for Science

**Photo**: Professor Chen Ning Yang receives his prize from
HRH Prince Abd Allah ibn Abd Al-Aziz,
The Crown Prince, Deputy Chairman of the Council of Ministers
And Head of the National Guard

# SYNOPSIS OF ACHIEVEMENTS

C. N. Yang was born on September 22, 1922 in Hefei, Anhui, China. His father, W.C.Yang, (also known as K.C.Yang), was a high school teacher at that time. A year later the elder Yang went to the USA for his Ph.D. degree, and came back to China in 1928. He became a Professor of mathematics at Tsinghua University in Beijing in 1929. It was on the campus of this university that the young Yang spent eight boyhood years, going first to elementary, then secondary schools.

In July 1937, the Japanese invaded China and the Yang family moved to Kunming, a remote southwestern city famous during the wartime as the terminal point of the Burma road through which gasolene and guns were shipped to China. It was in Kunming that C.N. Yang began his career as a physicist, by first enrolling at the Southwest Associated University as an undergraduate, earning a B.Sc. degree in 1942, then studying graduate physics at the same university, earning a M.Sc. degree in 1944. Material conditions during the wartime years in China were extremely difficult. But Yang made great progress in his studies. He later wrote in 1982 with obvious deep emotions,

> "Thinking about my student days in China, I am moved by the memory of the atmosphere of the Southwest Associated University, which provided an opportunity for me to learn and to grow. In retrospect, my taste in physics was largely formed during the six years (1938-1944) I spent at that university."

In August 1945, Yang started on his journey to the USA to pursue his Ph.D. degree. It took him three months via India, the Suez canal and the Atlantic ocean to arrive at New York City on November 24, 1945. He had planned to study for his degree and then go back to China to teach, as his father had done some twenty years earlier. Providnece intervened, however, and he had remained in the USA throughout his later research and teaching career.

Yang studied with Fermi and Teller at the University of Chicago. He later wrote that his Chicago years were of crucial importance in showing him what problems to choose to attack. He got his Ph.D. in 1948 and moved to the Institute for Advanced Study in Princeton in 1949, where he was to spend his peak years of research output. In 1966 he left the Institute for the State University of New York in Stony Brook. About this move he later wrote in 1982.

> "I had spent seventeen years, 1949-1966, at the Institute for Advanced Study, from age 27 to age 44. I had been productive and happy there. I liked its unpretentious Georgian buildings and its peaceful, restrained atmosphere. I liked its long, meandering walk to the little suspension bridge in the woods. It was a place outof this world.

It was a place meant for contemplation, and it was populated by people who contemplated well. The permanent faculty was first class. The visitors were generally brilliant. It was an ivory tower in the best sense of the term.

I could not escape asking myself sometimes, during that period of moving, whether I was making the right decision to leave the Institute for Advanced Study. But the answer was always the same. Yes, it was the right decision: The ivory tower is not the world, and the challenge to help build a new university is exciting."

Yang spent the next 33 years as Einstein Professor at Stony Brook. He retired in 1999. But he remains as Distinguished Professor at Large at the Chinese University of Hong Kong, a post he occupied since 1986.

# SUMMARY OF SOME CONTRIBUTIONS TO THEORETICAL PHYSICS

**C. N. Yang**

State University of New York, Stony Brook, New York, USA
Chinese University of Hong Kong

My most important contributions to physics are in the following three areas:

[A] **Yang-Mills theory**. In 1953 while visiting the Brookhaven National Laboratory, I formulated with R.L. Mills the non-Abelian gauge field theory, later called Yang-Mills theory.[1]

The Yang.Mills field is different from Abelian gauge field (electromagnetic field). It is based on the non-Abelian gauge principle. It naturally contains non-linear interactions. The field strength is

$$F^a{}_{\mu\nu} = \partial B^a{}_\mu/\partial x_\nu - \partial B^a{}_\nu/\partial x_\mu + gC_{abc}B^b{}_\mu B^c{}_\nu. \qquad (1)$$

The Lagrangian is

$$\mathcal{L} = -\frac{1}{4}F^a{}_{\mu\nu}F^a{}_{\mu\nu}. \qquad (2)$$

The interaction of this field with other fields is governed by the gauge principle. When I was a graduate student at Chicago, I was already intrigued by the relationship between charge conservation and invariance under phase transformations. At that time, many particles had been discovered, and their interactions had seemed very complex. I thought that one must find a principle to determine such interactions. I tried to generalize the phase transformation principle to apply to isospin conservation, but did not succeed after many attempts due to failure to include the last term in equation (1). I returned to the idea when visiting Brookhaven during 1953-1954. Mills, a Columbia doctoral student working with Professor N. Kroll, was also visiting Brookhaven and shared an office with me. Mills was close to finishing his Ph.D. dissertation. I invited him to collaborate on the problem. By February 1954 we had basically finished the project. Our paper was completed in June and was published in the *Physical Review* in early October.

This paper introduced the concept of non-Abelian gauge invariance and the related gauge field theory. It was an epoch-making contribution, laying the foundation, and supplying the fundamental principles and fundamental equations, for the whole of particle physics: There exist four types of interactions in nature: strong, electromagnetic, weak and gravitational. It is now known that the fields transmitting these interactions are all Yang-Mills fields.

It is especially appropriate to point out, here in Saudi Arabia, that gauge theory is the theory that gives the precise mathematical structure of fundamental forces in terms of *symmetry*. Now *symmetry*, in fact, is an ancient concept, and has played important roles in the culture of all civilizations. In particular, Islamic architecture is especially distinguished for having extensively exploited this basic esthetic concept in intricate ways.

[B] **Parity nonconservation in weak interactions.** In the mid-50's particle physics was a hot field. Major research efforts were devoted to understanding the properties of newly discovered particles: their charge, spin, mass and decay, etc. Out of such research, there emerged the so-called $\theta$ — $\tau$ puzzle: $\theta \to \pi\pi$ and $\theta \to \pi\pi\pi$ were believed at the beginning to be two different particles, because according to the simplest ideas they were given different parities. This idea later appeared to be consistent with much experimental data, and it was concluded that $\theta$ and $\tau$ were indeed two different particles. On the other hand, many other experiments indicated that they ought to be the same particle. This led to the $\theta$—$\tau$ puzzle. During 1953-1956 this problem was gradually recognized as a key problem in particle physics. There were off-the-cuff suggestions that parity was not conserved and that $\theta$ and $\tau$ were the same particle. But that ran against hundreds of $\beta$-decay experiments proving parity conservation.

One day in late April or early May in 1956, a key idea occurred to me and T.D. Lee at our lunch in a Chinese restaurant in New york City. It was: parity nonconservation *only* in the weak interactions. Two to three weeks after that lunch, through many calculations, we proved that *all previous $\beta$-decay experiments were in fact too simple to test parity conservation in $\beta$-decay*. Thus parity conservation in weak interactions was in fact an open question and we proposed several experiments to test it.

Our reprint was finished in June 1956 and was later published[2] in the *Physical Review*. It was not well-received. In a famous letter to V. Weisskopf, Pauli wrote: "I do not believe that the Lord is a weak left-hander..." Experimental physicists generally did not want to try the proposed experiments because none of them appeared to be simple. Furthermore, they were skeptical that our proposal would solve the $\theta$ — $\tau$ puzzle.

Chen-Shiung Wu of Columbia University was a great authority on $\beta$-decay experiments. She was one of the few experimentalists who realized the importance of the proposed experiments. She decided to collaborate with four low-temperature physicists from the National Bureau of Standards to do one of the experiments we had proposed. Half a year later, in early !957, Wu made public their results. Parity is *indeed* not conserved in $\beta$-decay. This striking discovery was a shock to the whole physical community. Since $\beta$-decay is only one type of

weak interaction, one should test parity conservation in all other types of weak interactions we had suggested. Many laboratories rushed into this and verified within a couple of years that indeed parity is not conserved in all weak interactions.

For our achievement, we were awarded the !957 Nobel Prize in Physics. Our work also directly or indirectly focused particle physicists' attention in the next decade on various aspects of symmetry.

[C] **Yang-Baxter equation.** In !967, I published a paper[3] on the following extremely simple one-dimensional quantum many-body problem:

$$H = \sum_i p_i^2 + 2c \sum_{i>j} \delta(x_i - x_j). \qquad (3)$$

I found that this problem is completely solvable. A key point is the following important equation

$$A(u)B(u+v)A(v) = B(v)A(u+v)B(u) \qquad (4)$$

where A(μ) and B(ν) are square matrices and μ and ν are variables. From equation (3), I obtained two matrices A(μ) and B(ν) which do satisfy equation(4). Using equation (4) I then proved that the original many-body problem (3) is completely solvable. In 1972 R.J. Baxter, while studying some classical statistical mechanical problems in two dimensions, also noticed the importance of equation (4), which was named in 1981 the Yang-Baxter equation. In later years, people have discovered further and deeper significance of this equation in mathematics and in physics. It is one generalization of the permutation group, and is likely to play further important roles in future developments.

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2001 winners meet HRH Prince Abd Allah ibn Abd Al-Aziz,
The Crown Prince, Deputy Chairman of the Council of Ministers
and Head of the National Guard
Prior to the official awards ceremony.

**L** to **R**: Professor Chen N. Yang, Professor Ibrahim A. Al-Saafin, Professor Mansour I. Al-Hazmi, HRH Prince Charles, HRH Prince Abd Allah ibn Abd Al-Aziz, HRH Prince Salman ibn Abd Al-Aziz, Professor Thomas E. Starzl, Professor Sir Roy Y. Calne, Professor Sajeev John

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