THE ECHO FOUNDATION

presents

The Aaron Ciechanover Project: Living Science

Student Dialogue
April 5, 2011

hosted by
William A. Hough High School
12420 Bailey Road
Cornelius, North Carolina
Dear Teachers,

This year, through the template of science, coupled with The Echo Foundation’s commitment to creating a more humane world, The Aaron Ciechanover Project: Living Science promotes personal responsibility and offers opportunities for students and teachers alike to investigate a specific area of science and its far-reaching applications. The beauty and creativity inherent in scientific exploration opens up a universe of discovery for students as they come to learn from one of the great scientific minds of our time. What responsibility do we each bare, if not to contribute those talents which are our own to the service of humankind?

The world urgently needs knowledgeable, responsible, and ethical leaders of tomorrow who will work toward the peaceful and dignified existence of all people. We thank you, teachers, now and always, for your commitment to incorporating social awareness into your daily lessons and shaping those who will direct the future.

With wishes for a rewarding and inspired year,

Stephanie G. Ansaldo, President
The Echo Foundation
The Aaron Ciechanover Project: Living Science

Photo courtesy of Technion-Israel Institute of Technology

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The Aaron Ciechanover Project: Living Science

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“The longer I am in science, the more I am in love with it. My love for science has never stopped but, on the contrary, has always deepened and broadened; it's an endless love story.”

--Dr. Ciechanover, in an interview for Rambam On Call, a publication of Israel’s largest medical center Rambam Health Care Campus
Autobiography

By Dr. Aaron Ciechanover
Excerpted from www.nobelprize.org
2004

The formative years - childhood in the newly born state of Israel

I was born in Haifa, a port city in the northern part of Israel, in October 1947, one month before Israel was recognized by the United Nations (UN) as an independent state. It took several additional months to establish the necessary institutions and for the British to leave, and on May 15th 1948, David Ben-Gurion, the founding father of the modern Jewish state and its first Prime Minister, made Israel a fact and declared its establishment as a democratic state and a home for every Jew in the world. The neighboring, but even more distant Arab countries, along with powerful Arab parties from within, did not accept the UN resolution and deliberately decided to alter it by force. A bloody and costly war erupted. It lasted a year, and more than 1% of the population of the newly born and defenseless state sacrificed their lives on its defense. I assume that the first two years of my life (1947-1949) were extremely difficult for my parents, Bluma (nee Lubashevsky) and Yitzhak, who immigrated from Poland with their families as adolescents in the mid-1920s. Why did their families leave Poland - their "homeland" - their houses, working places, property, relatives and friends, and decided to make their new home in a place with a vague, if any, clear future, that was part of the British Empire? They were idealists who enthusiastically followed the call of the Zionist movement that was established at the turn of the century by Benjamin Ze'ev Herzl - the seer of the Jewish State - to settle the land and make it - after two thousand years in the Diaspora, since the destruction of the temple in Jerusalem - a home for the Jews. Following the Jewish Congress in Basel (Switzerland) in 1896, Herzl declared: "In Basel I founded the Jewish State". At that time Israel was part of the Ottoman Empire and became in 1917 part of the British Empire. My parents came from religious families, and the move, I believe, had also religious roots: Jews, throughout their lives in the Diaspora, have not stopped dreaming of having their own country, with Jerusalem as its capital, a dream that was driven by a biblical decree and prophecy: "Thus saith the Lord GOD: Behold, I will take the children of Israel from among the nations, whither they are gone, and will gather them on every side, and bring them into
their own land" (Ezekiel 37:21); "And they shall dwell in the land that I have given unto Jacob my servant, wherein your fathers dwelt; and they shall dwell therein, they, and their children, and their children's children, for ever" (Ezekiel 37:25); "And I will rejoice in Jerusalem, and joy in my people; and the voice of weeping shall be no more heard in her, nor the voice of crying" (Isaiah 65:19).

The question of timing was an important one, as despite centuries of continuous persecution and discrimination in Europe, the initial idea to establish a Jewish State had been the dream of a few. Only small groups of Jews settled in Israel during the 18th, 19th, and the beginning of the 20th century. It was only towards the end of the 19th century, with the ideas of Herzl and the moves that led to the Balfour declaration (the British Minister of Foreign Affairs, who declared in 1917 the recognition in the need for a Jewish homeland), that an active Zionist movement and institutions were established, resulting in the translation of the dream into reality. Yet, it took an enormous amount of courage and daring by these European Jews to materialize this dream and try to establish, with almost no resources or support, a homeland in a place they had dreamt of for two thousand years, but that was not theirs at the time. The process was clearly accelerated by the heavy clouds that then covered the skies of Europe and that ended with the Holocaust. Many members of my parents' families immigrated to Israel before the Holocaust, but those who remained in Poland were perished by the murderous German and their loyal Polish collaborators. The conversion of this movement into a State at that particular time (1947-1948) was no doubt the direct historical result of the holocaust, and symbolized the rise of the Jewish Nation from ash.

My father was a clerk in a law firm (later - along with my brother - he studied law and became a lawyer), and my mother was a housewife and English teacher. My brother, Joseph (Yossi), who is 14 years older then me, was already on his national military compulsory service when I was 4 years old, the age from which I remember myself. I grew up in Haifa and enjoyed the wonderful beaches and Mount Carmel that rolls into the Mediterranean Sea. From my early days at home I remember a strong encouragement to study. My father worked hard to make sure we obtained the best possible education, and at the same time he was a member in the "Hagannah" (defense), one of the pre-state military organizations that fought the British for an independent Jewish State. Working in a law firm in the Arab section of the city, he risked his life daily going to work during the pre independence war hostilities and then the war time. My brother told me the family was waiting daily on the balcony to see him returning home safely. At home he used every free minute to delve into classic literature, Jewish religious law (Mishnah and Talmud) and modern law books. An important part of the education at home involved Judaism and Zionism. On the Jewish side we obtained a liberal modern orthodox education. We attended services in the synagogue every Saturday and during holidays, and celebrated at home all Jewish feasts. Needless to say that my mother kept a kosher kitchen. It was extremely important for my parents to educate us as a new breed of proud Israeli Jews in their own independent country. My father
inherited me with his love of Jewish studies and cultural life. To this very day, along with several physicians and scientists colleagues, I take regular lessons taught by a rabbinical scholar, on how the Jewish law views moral and ethical problems related to modern medicine and science. Jewish cantorial music reflecting prayers of Jews along many centuries has become my favorite music, and I avidly search for this vanishing vocal expression of Jewish culture in flea markets, used records stores, and auctions all over. Also, different Judaica artifacts decorate my study. In parallel, my parents made sure we should receive an excellent general education. My father spoke fluently several languages, Hebrew, Polish, Arabic, French, English, German and Yiddish, and wanted me to acquire his strong love for books: while our home was not a rich one, we had a huge library. My parents also loved classical music, so we had a great collection of 78 rpm, and later 33 rpm records. The apparently peaceful life of our family in Israel (although under the British Crown) during the years of the Holocaust in Europe (1939-1945) were overshadowed by the murder of their family members and of many families of their relatives and friends that did not escape Europe in time. For my parents, the establishment of the State of Israel as an independent and sovereign Jewish State was a direct historical result of the Holocaust in Europe and a clear statement of "Never Massadah shall fall again" (Massadah was one of the last strongholds of Jews during the Roman Empire. It fell into Roman hands after a long curfew during which all its defenders committed suicide in order not to fall as prisoners in Roman hands. While asiring for freedom, they lost their land and lives. They were not ready to live anywhere or under any circumstances, but as free people in their own land). They left us with the idea that the Jewish State will not only protect us as a free people, but will allow us to develop our own unique culture in a more general national context, rather than as minorities scattered in different countries in the Diaspora.

**Falling in love with Biology**
From early days I remember my strong inclination towards biology, though it has taken different directions at different times. I remember collecting flowers on Mount Carmel and drying them in the heavy Babylonian Talmud of my brother. I will never forget his rage at discovering my love of nature hidden among the pages of the old Jewish tracts. Then came the turtles and the lizards, and extracting chlorophyll from leaves with alcohol, and the first microscope my brother bought me from his trip to England when I was 11 years old. With this microscope I discovered cells (in the thin onion epithelium) and did my first experiment in osmosis, when I followed the alteration in the volume of the cells after immersing the epithelium in salt solutions of different strengths. With friends we tried to launch a self propelled rocket. The flowers collection kept growing, now in special dedicated albums, and with it, a small collection of skeletons of different animals - fish, frog, snake, turtle, and even some human bones I received from an older friend who was a medical student. After several years of amateurish flirting with biology, I decided to formalize my knowledge and love of biology, and to major in biology in high school. While my years in elementary (1953-1959) and junior high school (1959-1963) were mostly uneventful and passed
without any thoughts on my future, the last two years in high school in Haifa (1963-1965) were not. I had wonderful and inspiring teachers in biology, chemistry, physics and mathematics who revealed to me a little of these different and exciting disciplines. Yet, I felt that twice as much was still concealed. Biology at that time was largely a descriptive area. While we studied the mechanism of conversion of glucose to H₂O and CO₂ and the production of energy in yeast and mammals (and the opposite process occurring during photosynthesis in plants), and became acquainted with simple graphic descriptions of mitotic and meiotic cell divisions, most of our studies were devoted to detailed descriptions of the flora and fauna in our region, to comparative zoology (I remember well the efforts invested in memorizing the twelve differences between the frog and the toad, or between the circulatory systems and skeletal structure of the cat and dog), and to basic descriptive human anatomy and physiology (e.g. how the human skeleton structure enables posture on two limbs). Pathogenetic mechanisms of diseases had not been taught, and the structure of DNA and the genetic code had entered our textbooks only towards the end of our high school studies, in 1964/5. On the other hand, chemistry and physics appeared to me, maybe naively, strong mechanistic disciplines built on solid mathematical foundations. As a result, I had a deep feeling that the future somehow resided in biology, in deciphering basic mechanisms, as so little was then known. Yet, the complexity of biological and pathological processes looked to me enormous, almost beyond our ability to grasp, and I was intimidated: while I was clearly attracted to the secrets of biology, I was afraid to get lost. Importantly, I had nobody around, close enough, to consult, to clarify my thoughts. While deliberating between the largely unknown in biology and what I naively thought were the already well founded physics and chemistry, medicine emerged as a compromise: it appeared to me as representing a balanced mixture of physics, chemistry, basic biology and physiology, along with interesting pathology and social sciences.

Adding to this complexity was that during these years I lost both of my parents: my mother died in 1958 and my father in 1964. After the death of my mother, I was left with my father who took wonderful care of me. When my father died several years later, my late aunt Miriam (Wishniak; my mother's sister), with the help of my brother and sister-in-law, Atara, took me to her home in Haifa, enabling me to seamlessly complete my high school studies in the same class and along with my friends - without interruption. The other option was to move to Tel Aviv, to my brother's home, but this would have been much more complicated. So I spent the weekdays with my aunt in Haifa, studying, and the weekends and holidays with my brother and sister-in-law, in Tel Aviv. Their help was a true miracle, as thinking of it retrospectively, being left
alone without parents at the age of sixteen, the distance to youth delinquency was shorter than the one to the high school class. Yet, with the help of these wonderful family members, I managed to continue.

**How my love of biology evolved to become a career**

Towards graduation from high school I had to make a decision. The regular track would have taken me, like most Israelis, to national compulsory service in the Israeli Defense Forces, IDF, a duty we were all eager to fulfill. In addition to the regular service, the army encourages certain high school graduates to postpone their service and first obtain a university education, particularly in areas that are relevant to the military, such as medicine and different disciplines in engineering and science. Lacking any financial support, I thought it would be better to acquire a practical profession I could make a living from as soon as I could. As I mentioned, medicine emerged as a compromise between the complexity and mysteries of biological mechanisms to what I thought are the already well founded physics and chemistry. Not less important, medicine has traditionally been the ultimate in "Jewish" professions, the dream of every Jewish mother and family. What also attracted me to medicine is that I was under the impression that diseases can be cured: as children, we may have been influenced by short, self-limiting diseases that affected us, like influenza and measles, and were not directly aware of the major killers that left physicians and scientists alike helpless (much like these days), such as malignancies, vascular diseases and neuro-degenerative disorders: I had not appreciated at the time how far more descriptive medicine is, much more than biology. Practically and not less important (which helped solve my dilemma), was the fact that biology was not an option in this military-supported service postponement program. Last but not least, it was a practical choice, a profession one can make a living on. So, after a fierce competition I was accepted into the only medical school in Israel at that time, that of the Hebrew University and "Hadassah" in Jerusalem (1965). The first four years (1965-1969) were exciting. We studied basic and clinical sciences, and I started to seriously entertain the idea of broadening my knowledge base in biochemistry or pharmacology. Towards the end of the 4th year, once we started to examine patients, serious doubts had begun to arise whether I made the right choice and truly want to become a practicing physician. The imbalance between phenomenology and pathogenetic mechanisms of
diseases on one hand, and the lack of any mechanism-based treatment for most of the major killers on the other hand, made me seriously think that I was on the wrong trail. I felt restless and started to realize how little we know, how descriptive is our understanding of disease mechanisms and pathology, and as a consequence how most treatments are symptomatic in nature rather than causative. The statement "with God's help" that I heard so frequently from patients that were praying for cure and health, took on a real meaning. I had a feeling clinical medicine was going to bore me, and decided to take one year off in order to "taste" true and "wet" basic research. The Faculty of Medicine had a special, one year program for the few who elected to broaden their knowledge in basic research, and I decided to major in biochemistry. I had to convince my brother that this was the right thing to do, as I needed his help to further postpone my military service by one year. This was not easy, as he too had a "dream" - to see me independent with a profession from which I could make a living, and which in the traditional Jewish spirit was nothing else but practical medicine. Following our parents' death, he felt he was responsible for my future and well being, and wanted to see me professionally and financially independent as soon as he could. I nevertheless managed to convince him, and during that year (1969-1970), [I performed research] under the guidance of excellent biochemists, Jacob Bar-Tana and Benjamin Shapira. Completing this research year (and obtaining a M.Sc. degree), I knew I had found a new love - biochemistry. Jacob and Benjamin walked me through the exciting maze of biochemical pathways, and I was mystified. Yet, the consummation was still far away. Being loyal to the promise I made to my brother, and also to my commitment to the Israeli army, I completed the clinical years (1970-1972) and graduated from Medical School.

To obtain my medical license, I still had to complete one additional year of rotating internship. At that time, colleagues told me that a young talented biochemist, Dr. Avram Hershko, had just completed his post-doctoral training and was recruited by the Dean and founder of the newly established Faculty of Medicine at the Technion in Haifa, the late Professor David Ehrlich, to establish a Unit of Biochemistry. I wrote to Avram, with the intention to relocate to Haifa, to carry out my rotating internship there, and to use this year to complete my M.D. research thesis under his supervision. This was a small thesis I had to submit to the Medical School in partial fulfillment of the requirements for graduation. Typically for this thesis, most medical students are evaluating statistically on-going treatments/procedures, but I decided to return to the
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laboratory and touch on yet another research project in biochemistry. Avram agreed to accept me as an M.D. research student, and in October 1972 we started our more than three decades voyage. Avram was still not certain about his own main research direction, and we discussed two possibilities for my M.D. thesis. The year (1972-1973) I spent in the laboratory (it was not a real year but rather moon lighting, as a significant part of the time I was busy in the hospital, rotating among the different clinical departments, completing my internship and duties towards graduation. I worked in the laboratory in my free evenings, nights, weekends and holidays) finally convinced me to pursue a career in Biochemistry. But I still had three years of military service ahead of me (1973-1976).

My military service and professional career - have they collided with one another?

Following graduation, it was time to repay my national debt and serve in the IDF. I served for three years (1973-1976) and did it gladly. Serving in the army has always been regarded as an integral and important part of Israeli life, and an entry card to its society, giving one the feeling of sharing - everyone takes part in protecting this land and its inhabitants. In addition, the service itself was extremely interesting, technically, but also socially and historically. Technically, since I served in interesting units. Socially, since the military service is a wonderful humane experience, the best melting pot one can go through, generating true friendships during hard times, friendships that are therefore deep, true and lasting. Historically, it spanned an interesting period. Initially I served in the navy, as a physician in the missile boats fleet. The year was 1973, immediately after the October Day of Atonement (Yom Kippur) war, and Israel faced a problem of protecting its southern gates, the Red Sea and the marine entry to its port in Eilat. Marine transportation through the southern gates of the Red Sea, Bab-el-Mandeb strait, and the narrow Tiran (Sharm-a-Sheikh) strait were threatened by the Arab countries that neighbored the water way, mostly Saudi Arabia and Egypt, but also Yemen and Somalia, and Israel had to stretch its marine arm. To do so, it was necessary to transfer missile boats from the main naval bases in the Mediterranean to the Red Sea. At that time Israel did not have diplomatic relations with Egypt, and the Suez Canal was blocked by ships sunk by the Egyptians during the June 1967 Six Day War. Thus, the decision was to bring the boats from Haifa to Eilat, sailing via the Mediterranean Sea, the Gibraltar strait and around the West and then East coasts of Africa. I was the physician of the "Reshef", one of the two modern Israeli missile boats that were built in the Haifa naval shipyard. One can imagine that for small missile boats, such a long, several weeks voyage, a large part of it in the open
Oceans, is rather complicated, and for many reasons also risky. Beyond fuelling and provision of supplies and spare parts to the crews and boats, one has to think of sailing in waterways surrounded by hostile countries, many miles away from home and a long flight distance for the Israeli Air Force. Another problem was obviously medical, how one treats emergencies, from possible gunshot wounds through "simple" daily problems like appendicitis, in a small ship, far from any medical facility and with limited diagnostic and treatment capabilities. I was particularly concerned, as I was a young physician with almost no clinical experience. I assume this would have been a challenge for more experienced physicians as well. Luckily, the voyage was smooth. The remaining part of my three-year service was also interesting. I spent that time in the Research and Development unit of the Medical Corps, developing a broad array of sophisticated devices for the soldier in the battlefield. Because of the broad range of experiences acquired, the military service has been my ever best school for real life "sciences". During all these years (1973-1976) I maintained tight connections with Avram and fulfilled my duties as an "external" department member: during vacations from the military, and along with other members of the department that grew meanwhile, I taught continuously the course in Clinical Biochemistry to 3rd year medical students. I should mention in particular Michael (Mickey; see also below) Fry, with whom I have remained a good friend to the very present. Also, in 1975, during the military service, I married Menucha, a physician and a graduate of Tel Aviv University School of Medicine. Menucha was a resident in internal medicine in Tel Aviv Municipal Hospital, and we built our first home in this city. Marrying Menucha brought my wanderings to an end, and I felt I had again a family and a home. During all the years since the death of my father (1963-1975), I did not have a real stable home, and I wandered between the homes of my brother and sister-in-law in Tel Aviv and of my aunt in Haifa. They were truly wonderful, but I needed a base, and Menucha, with her quiet approach and warm acceptance, along with our beautiful apartment, provided me with this, so much needed, shelter.

Towards the end of the military service, I had to make what I assume has been the most important decision in my career: to start a residency in clinical medicine, in surgery, which was my favorite choice, or to enroll into graduate school and start a career in scientific research. It was clear to me that I was heading for graduate school. My disillusionment from clinical medicine that diseases can be cured based on understanding their pathogenetic mechanisms, along with a magical and enchanting attraction to biochemistry made the decision easy. I received a strong support and encouragement from my wife Menucha, who started to realize she was married to a student in sciences with no clear future rather than to the physician with a bright career and broad financial horizons that she thought she had married. So in November of 1976, after my discharge from the national military service and a two-month driving trip across the USA, I started my graduate studies with Avram Hershko…
Post-graduate training at MIT and how I continued my studies on the ubiquitin system independently

The five years in graduate school had a significant impact on my future career. Not only because I played an active part in the discovery of such an important pathway, but maybe more important, because I learnt several basic and key principles on how to approach a scientific problem. From my mentors I learnt two principles: first, to select an important biological problem, preferably an unobvious one and not in the mainstream, and second, to make sure that there are appropriate research tools to approach it experimentally. I also learnt to become a long books author rather than a short story writer: I learnt not to be opportunistic but rather to adhere to a project, to dig deeply into a problem, to resolve it mechanistically, to unravel complex mazes - peeling them like an onion, not to be tempted to be dragged after fashions. I learnt to pay attention to small details, to carefully examine hints, as the important findings are not always obvious from the apparent results. I learnt to be stubborn, to fight difficulties uphill, but most importantly, to be critical: I believe I developed good senses that enable me to distinguish false from truth, and artifacts from meaningful findings. Interestingly, I learnt all these principles not in frontal lessons or formal presentations, but as an apprentice, following my mentors' own attitude and way of thinking. At the same time I also learnt to question, to doubt, to ask, and to discuss, to follow my own gut feeling when it was necessary, not to always take advice and direction for granted, and to trust myself too. It did help in many occasions along the way. Thus, at times I found myself swimming alone against the stream. Altogether, these principles generated an important philosophy and shaped my approach to science, something I try to instill in my own students, as I strongly believe it is the only way one can make an impact, leave an imprint behind.

Towards graduation I had to think of the next step - post-doctoral training and planning of my future career as an independent scientist. I was in a dilemma. On the one hand, I knew it was important to obtain training somewhere else, under different mentorship, in a different environment, being exposed to a different culture of science. On the other hand, I knew for certain that the ubiquitin system was extremely important and that we were seeing only the tip of its iceberg. I therefore wanted to continue my studies in a related field, learning more on regulated proteolysis, but also to continue my own studies on ubiquitin. I had several ideas in mind on where to go, but the choice was quite narrow and also risky, as I did not have any idea of how much independence I could have as a post-doctoral fellow. Searching for a mentor, and with the advice of my colleague Mickey Fry, I looked for scientists whose work was related to regulated proteolysis. I wrote to Günter Blobel in the Rockefeller University, who worked at that time on translocation of proteins across the endoplasmic reticulum (ER) membrane, a process that involves cleavage of the leader peptide by signal peptidase, to Jeffrey Roberts in Cornell University who worked on E. coli RecA protein-directed cleavage of phage λ repressor and its requirement for polynucleotide, and to Harvey Lodish at the M.I.T. who worked, among other subjects, on processing of viral polyproteins. I am not sure Harvey was that impressed with the ubiquitin system at that time, but he was the only one to respond positively. Typical of his etiquette (as I learnt later), his response was prompt and direct, and he invited me for an
interview after which he accepted me. Günter was kind enough to let me know he did not have space in his laboratory at that time, and Jeffrey never responded.

With two fellowships, one from the Leukemia Society of America and one from the Israel Cancer Research Fund, ICRF, I started a period of three wonderful years (1981-1984) in Harvey's laboratory in the Department of Biology at M.I.T. Harvey gave me complete freedom to choose my research subjects. What I had in mind was to take advantage of the exceptional strength of the laboratory and Harvey's unique expertise in cell biology, but in parallel, to continue my own studies on the ubiquitin system…

The return to Israel - independent research career
After three years at M.I.T. (1981-1984), it was time to seek for an independent academic position. After many deliberations and despite attractive offers and a strong temptation to stay in the US, I decided to return home, to Israel. With the help of Avram, I obtained an independent academic position in the Department of Biochemistry at the Faculty of Medicine of the Technion (where I graduated), and returned home towards the end of 1984, after a productive post-doctoral period. Importantly, I already had a research subject I wanted to pursue, the effect of RNase on ubiquitin-mediated proteolysis.

The years that followed the post-doctoral fellowship (1984-present) have been extremely rewarding. I was happy to return to Israel, to my family and friends, to a place I felt I belong. I established my own independent research group and laboratory, obtained extramural competitive funding, and continued my research on the ubiquitin system. I have been lucky to have, along the years, a group of extremely talented graduate students and post-doctoral fellows. These years have not been simple, however. The Technion has traditionally been a school of engineering, and life sciences and biomedicine have been foreign to many of its senior leaders, faculty members and policy planners: we were treated in many ways like step children, and thoughts of closing the medical school have been aired at times. This deeply rooted philosophy, which only now starts slowly to change, has severely hampered development in these fields and had left the body of researchers and infrastructure in these areas small and battling for survival. Unlike leaders in other schools of engineering like M.I.T. and Caltech, the Technion's leaders failed to foresee the upcoming revolution in biology and medicine and its huge impact on modern technology. However, through a network of wonderful colleagues all over the world…and fruitful collaborations, I was able to establish an active research group and carry out what I believe was a good and original research program, even under less than optimal, and at times impossible conditions. This was important in balancing my desire to live in Israel, but at the same time to remain at the forefront of the ubiquitin research field that has grown in its importance to become an extremely exciting, yet a highly competitive, area…
Membership Organizations

From “Dr. Ciechanover - Curriculum Vitae.” Cancer and Vascular Biology Research Center, The Technion.

Academic Boards
2006: Institute of Advanced Studies, Hong Kong University of Science and Technology
2006: Scientific Advisory Board, Britton Chance Center for BioMedical Photonics, Huazhong University of Science and Technology, Wuhan, China
2008: President’s Council, New York Academy of Sciences

Editorial Boards
1999: Israel Medical Association Journal
2006: Experimental Biology and Medicine
2007: Cell Death and Differentiation (Nature Group)

Academic Memberships
1996: Council of the European Molecular Biology Organization
1999: Asia-Pacific International Molecular Biology Network
2004: European Academy of Sciences and Arts
2004: European Academy of Sciences
2004: Israel Academy of Sciences and Humanities
2004: Honorary Member, American Chemical Society
2005: Honorary Fellow, Royal Society of Chemistry, United Kingdom
2005: Foreign Member, American Philosophical Society
2006: Honorary Member, Society for Experimental Biology and Medicine
2006: Fellow, Federation of Asian Chemical Societies
2007: Polish Academy of Medicine
2007: Albert Schweitzer World Academy of Medicine
2007: National Academy of Science and Technology of South Korea
2007: Foreign Associate, National Academy of Sciences of the USA
2008: Pontifical Academy of Sciences, The Vatican
2008: The Council for the Advancement of the United States-Israel Binational Science Foundation
2008: Honorary Member & Foreign Member, American Academy of Arts and Sciences
2008: Foreign Associate, U.S. Institute of Medicine, National Academy of Sciences of the USA
2009: Ukrainian Academy of Sciences

Non-Academic Honorary Memberships
2004: The International Raoul Wallenberg Foundation
2005: The World Innovation Foundation
2005: Academy of Achievement

Professional Memberships
1984: American Association for Advancement of Science
Awards, Honors, & Honorary Degrees


**Fellowships**
1981-1983: Leukemia Society of America, Massachusetts Institute of Technology
1981-1984: Fulbright Fellow, Massachusetts Institute of Technology
1983-1984: The Medical Foundation and Charles A. King Trust, Boston
1988-1989: American Cancer Society Eleanor Roosevelt Memorial

**Academic Awards**
1984: Research Career Development Award, Israel Cancer Research Fund
1999: The Austria Ilse and Helmut Wachter Prize, Innsbruck University, Austria (shared with Dr. Avram Hershko)
2000: Jewish National Fund Alkeles Award for Distinguished Scientific Achievements
2000: Albert and Mary Lasker Award for Basic Medical Research (shared with Dr. Avram Hershko and Dr. Alexander Varshavsky)
2001: The Michael Landau (Mifa’al Ha’Peis) Award in Medical Sciences
2002: EMET Prize in Life Sciences and Medicine (Israeli Prime Minister Prize for the Arts, Science, and Culture) (shared with Dr. Avram Hershko and Dr. Leo Sachs)
2003: Israel Prize for Biological Research
2003-2006: Japanese Society for Promotion of Science, Distinguished Scientist Award
2004: Nobel Prize in Chemistry (shared with Dr. Avram Hershko and Dr. Irwin Rose)
2009: Centenary Prize, Royal Society of Chemistry

**Academic Honors**
1996: Janet and David Polak Professor of Life Sciences, the Technion-Israel Institute of Technology
2002: Distinguished Research Professor, the Technion-Israel Institute of Technology
2003: Professor, Israel Cancer Research Fund
2005: Cell Stress Society International Medal and Distinguished Life Member
2006: Sir Hans Krebs Medal, Federation of the European Biochemical Societies
2006: Honorary Professor, Capital University of Medical Sciences, Beijing, China
2006: Honorary Professor, Peking Union Medical College, Beijing, China
2006: Honorary Professor, Chinese Academy of Medical Sciences, China
2007: Medical Magnus Medal, Polish Academy of Medicine
2007: Honorary Professor, Henan University, Keifang, China
2007: Honorary Professor, Nankai University, Tianjin, China
2007: Honorary Professor, First Teaching Hospital Medical School, XinJiang University, Urumqi, China
2007: Honorary Professor, 4th Military Medical University, Xi’an, China
2007: Honorary Professor, Shihezi University, Shihezi, China
2007: Honorary Professor, Jiaotong University, Xi’an, China
2007: Honorary Professor, Northwest University, Xi’an, China
2008: Honorary Professor, Nanjing University, Nanjing, China
Honorary Degrees
2001: Tel Aviv University, Tel Aviv, Israel
2004: Ben-Gurion University, Beer Sheba, Israel
2005: City University of Osaka, Osaka, Japan
2005: University of Athens, Greece
2005: National University of Uruguay, Montevideo, Uruguay
2006: Washington University, St. Louis, Missouri
2006: Cayetano Heredia University, Lima, Peru
2007: Hebrew University, Jerusalem, Israel
2007: Bar-Ilan University, Ramat Gan, Israel
2007: Albert Schweitzer World Academy of Science
2008: Weizmann Institute of Science, Rehovot, Israel
2008: Universidad San Francisco, Quito, Ecuador
2008: Universidad del Norte, Asuncion, Paraguay
2008: Angeles University, Angeles City, The Philippines
2008: University of New South Wales, Sydney, Australia
2009: Honoraris Causa, The Academic College, Netanya, Israel
2009: The National University of Cambodia, Phnom Pen, Cambodia
2010: The Government of the People’s Republic of China via Huazhong University of Science and Technology, Wuhan, China

Non-Academic Honors
2005: Honorary Citizenship, City of Haifa, Israel
2005: Sakura Award, City of Osaka, Japan
2005: Special Award, the Mayor of Osaka, Japan
2006: Honorary Citizenship, City of Montevideo, Uruguay
2006: Honorary Citizenship, City of Lima, Peru
2008: Honorary Citizenship, City of Quito, Ecuador
2008: Special Distinction for Contribution to Education, Minister of Education, Government of Ecuador
2008: Honorary Citizenship, City of Manila, The Philippines
2010: Gold Medal, Ministry of Education and Science, Armenia
The Dinner Companion

By Ashutosh Jogalekar
July 7, 2009

When you first meet Aaron Ciechanover, he appears to have the distracted air of a man who feels slightly inconvenienced to be in whatever situation has been apparently imposed on him. But this preoccupied demeanor belies a mind which is ready to hold forth on a disparate variety of topics with infinite verve and enthusiasm and which is not reluctant to be politically incorrect, provocative and utterly honest. And it hides a broad smile which is very readily revealed at the mention of a favourite incident or fact.

If there is one word to describe the Israeli doctor, biochemist and Nobel Laureate it's passion, and this passion is pronounced no matter what the topic of discussion; from protein degradation to languages and traveling, from politics to history. Whether we were talking about protein structure or Israel-Palestine relations, Ciechanover's thoughts were always opinionated, honest, cogent, provocative and without a dull shade in them. This is the kind of stimulating person that you always want as a dinner companion.

I met Ciechanover along with a small group of students for dinner at a charming restaurant on a path lined with cobbledstones somewhere close to Lindau's Inselhalle on Fischergasse street. As we shuffled around our tables to accommodate everyone, Ciechanover was joined across the room by his fellow Nobel Laureate and friend Peter Agre, whom we met earlier. Both Agre and Ciechanover joke that they are doctors who received the Nobel Prize for chemistry without having any reasonably good knowledge of chemistry. But the humor hides an aspect of chemistry that we have been emphasizing here for a while now; its extraordinary diversity and synergy with other fields that allows even people who may not be trained as chemists to make contributions to the subject.

Aaron Ciechanover shared the Nobel Prize for chemistry for one of those discoveries that are deep and long-lasting. As a rule the Nobel Prize is awarded to great discoveries and not great scientists. The greatness of all discoveries is naturally not alike. The discovery that Ciechanover made ranks among those great discoveries that are fundamental for understanding life. The reason why DNA or electron transport in biological systems or the genetic code are considered prize-winning discoveries are not only because they demonstrated something absolutely basic about living systems but because they are absolutely universal. DNA is the molecular basis of all of life. The genetic code similarly underpins every single organism's existence on our planet. Aaron

Dr. Ciechanover delivering a lecture at the Lindau Nobel Laureate Meetings in July 2010. Photo courtesy of Lindau Nobel Laureate Meetings.
Ciechanover's and others' discovery of ubiquitin-mediated protein degradation is similarly universal and constitutes the basic mechanism of protein waste elimination in all eukaryotes. This is as fundamental as you can expect a process to be. Until Ciechanover and his colleagues discovered this, protein degradation was considered to be a general and non-specific process that was of secondary importance to the main processes of life. But Ciechanover and his colleagues Avram Hershko and Irwin Rose discovered ubiquitin, a small protein that as the name indicates is ubiquitous in eukaryotes and crucially aids in the destruction of proteins which have outlived their utility in one way or the other.

Naturally Ciechanover likes talking about the story of how he heard about the prize. Ciechanover was getting into his car to go somewhere when his son came to tell him that somebody from Stockholm had left a message and asked to call him back. Since Ciechanover has many colleagues and friends in Stockholm, he assumed that it must be one of them and decided to wait until later to call back. It was when he returned after a few hours and called this person with the unfamiliar name that he heard about the news. Amusingly, it was just 5 mins before the official prize announcement and the Stockholm official who delivered the news had to hang up right away. While all this was happening Ciechanover's co-laureate Hershko had gone for a swim and had no mobile phone. The swimming suit clad Hershko was surprised to see a troupe of journalists and others gathered in front of his house when he returned after a couple of hours and wondered what was happening.

Ciechanover's love of storytelling extends to his own interests which involve reading biographies and history books as well as a medieval romance set in 17th century Italy. I was delighted to hear him mention Max Perutz's absolutely delightful collection of essays, "I wish I'd made you angry earlier" which I have read several times as one of his favorites. He also mentioned Harold Varmus's recent memoir; Varmus is one of President Barack Obama's chief science advisors.

The students gathered around the table constituted a diverse and eager lot. They included students from Norway, Sweden and Russia. They were researchers in diverse fields, from gene therapy to thermodynamics to astrophysics and all exhibited a love of science, traveling, languages and culture. All of them greatly appreciated the connection with students from other countries that the Lindau meetings provide. All of them were highly motivated and seemed to latch on to every word that Ciechanover was saying. Ciechanover in turn had a very lively interaction with the students and he answered their questions with gusto and emphatic consideration. I also briefly and productively talked to him about the clinical aspects of ubiquitin from a drug discovery viewpoint. There are some efforts underway to discover small molecule inhibitors of the protein, but considering its ubiquitous distribution in
the body the target may not exactly be druggable. However if not anything else, small molecules can at least serve as probes to investigate basic functions of the protein.

Ciechanover also emphasized the importance of liking what you do. In this he reiterated what Peter Agre had noted during his interview; that until you take risks and do what you like, there is no way to know whether you have succeeded or failed. You can take the safe road and settle for a safe life, but then you potentially miss out on doing something exceptional. Even if you don't do something exceptional you can still take pleasure in the process of learning and doing. That is the sheer, unadulterated joy of science. Ciechanover also reminisced about flip-flopping a little during his career since he enjoyed both treating patients and doing lab research. But he said he learnt a lot from both. Ciechanover also mentioned that one of the joys of scientific research is the joy of meeting old friends and researchers several times every year in interesting places around the world.

During the long, enjoyable and ambrosial dinner which included the local Lake Constance speciality catch Felchen and was followed by a succulent dessert of fruit and ice cream, Peter Agre kept on coming to our table to take good natured jabs at his friend and colleague. At one point he announced that he knows even less chemistry than Ciechanover. Perhaps the most amusing moment was when he offered to sing Tom Lehrer's delectable song about the elements. With a flourish, Agre launched into an almost perfect rendition of the piece. I have heard the song several times and yet cannot sing even the first stanza; Agre must have practiced the song quite well. Friend of Ciechanover that he was, Agre announced that the name of an unstable element that was not included in the song was 'Ciechanoverium'.

All in all, we had a wonderful time and a really enjoyable dinner with a man who did not mince his words and who provided us with a lot of instruction, information and infinite enthusiasm.
An Introduction to Dr. Aaron Ciechanover

Chapter Study Questions

1. What childhood experiences contributed to Dr. Ciechanover’s love of biology, and later, biochemistry?

2. Describe Dr. Ciechanover’s educational upbringing. Compare it to yours. What are the differences and similarities?

3. Put yourself in Dr. Ciechanover’s shoes. Explain how you would have responded to your academic obligations if you lost your parents. Would you have called it quits or would you have persevered? Explain.

4. Why did Dr. Ciechanover choose medicine as his primary field of study instead of pursuing his first love, biology? Has there ever been a time when you had to choose between two subjects that interested you? What were the two subjects? Which one did you choose and why?

5. At certain stages of his life as a student, mentors played key roles in helping Dr. Ciechanover decide which direction his career should take. Name the people whom Dr. Ciechanover would consider to be his mentors and explain how they influenced his life. Who are your mentors? In what ways have they shaped your life?

6. In his autobiography, Dr. Ciechanover discusses his time in the Israeli Defense Forces, which is compulsory for every Israeli citizen. What is your opinion of this method of military conscription? Do you think the United States should require all of its citizens to join the military for a specified amount of time? Explain why or why not.

7. In the article, “The Dinner Companion,” the author describes how Dr. Ciechanover believes “that until you take risks and do what you like, there is no way to know whether you have succeeded or failed.” Discuss this statement and what you think it means.
II. Historical & Religious Background

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“For me Judaism is a culture, a culture imbedded deep in the history of these people…”

--Dr. Ciechanover in a 2006 interview with the Vega Science Trust
On May 14, 1948, in Tel Aviv, Jewish Agency Chairman David Ben-Gurion proclaims the State of Israel, establishing the first Jewish state in 2,000 years. In an afternoon ceremony at the Tel Aviv Art Museum, Ben-Gurion pronounced the words "We hereby proclaim the establishment of the Jewish state in Palestine, to be called Israel," prompting applause and tears from the crowd gathered at the museum. Ben-Gurion became Israel's first premier.

In the distance, the rumble of guns could be heard from fighting that broke out between Jews and Arabs immediately following the British army withdrawal earlier that day. Egypt launched an air assault against Israel that evening. Despite a blackout in Tel Aviv--and the expected Arab invasion--Jews joyously celebrated the birth of their new nation, especially after word was received that the United States had recognized the Jewish state. At midnight, the State of Israel officially came into being upon termination of the British mandate in Palestine.

Modern Israel has its origins in the Zionism movement, established in the late 19th century by Jews in the Russian Empire who called for the establishment of a territorial Jewish state after enduring persecution. In 1896, Jewish-Austrian journalist Theodor Herzl published an influential political pamphlet called The Jewish State, which argued that the establishment of a Jewish state was the only way of protecting Jews from anti-Semitism. Herzl became the leader of Zionism, convening the first Zionist Congress in Switzerland in 1897. Ottoman-controlled Palestine, the original home of the Jews, was chosen as the most desirable location for a Jewish state, and Herzl unsuccessfully petitioned the Ottoman government for a charter.

After the failed Russian Revolution of 1905, growing numbers of Eastern European and Russian Jews began to immigrate to Palestine, joining the few thousand Jews who had arrived earlier. The Jewish settlers insisted on the use of Hebrew as their spoken language. With the collapse of the Ottoman Empire during World War I, Britain took over Palestine. In 1917, Britain issued the "Balfour Declaration," which declared its intent to establish a Jewish homeland in Palestine. Although protested by the Arab states, the Balfour Declaration was included in the British mandate over Palestine, which was authorized by the League of Nations in 1922. Because of Arab opposition to the
establishment of any Jewish state in Palestine, British rule continued throughout the 1920s and '30s.

Beginning in 1929, Arabs and Jews openly fought in Palestine, and Britain attempted to limit Jewish immigration as a means of appeasing the Arabs. As a result of the Holocaust in Europe, many Jews illegally entered Palestine during World War II. Radical Jewish groups employed terrorism against British forces in Palestine, which they thought had betrayed the Zionist cause. At the end of World War II, in 1945, the United States took up the Zionist cause. Britain, unable to find a practical solution, referred the problem to the United Nations, which in November 1947 voted to partition Palestine.

The Jews were to possess more than half of Palestine, although they made up less than half of Palestine's population. The Palestinian Arabs, aided by volunteers from other countries, fought the Zionist forces, but by May 14, 1948, the Jews had secured full control of their U.N.-allocated share of Palestine and also some Arab territory. On May 14, Britain withdrew with the expiration of its mandate, and the State of Israel was proclaimed. The next day, forces from Egypt, Transjordan, Syria, Lebanon, and Iraq invaded.

The Israelis, though less well equipped, managed to fight off the Arabs and then seize key territory, such as Galilee, the Palestinian coast, and a strip of territory connecting the coastal region to the western section of Jerusalem. In 1949, U.N.-brokered cease-fires left the State of Israel in permanent control of this conquered territory. The departure of hundreds of thousands of Palestinian Arabs from Israel during the war left the country with a substantial Jewish majority.

During the third Arab-Israeli conflict--the Six-Day War of 1967--Israel again greatly increased its borders, capturing from Jordan, Egypt, and Syria the Old City of Jerusalem, the Sinai Peninsula, the Gaza Strip, the West Bank, and the Golan Heights. In 1979, Israel and Egypt signed an historic peace agreement in which Israel returned the Sinai in exchange for Egyptian recognition and peace. Israel and the Palestine Liberation Organization (PLO) signed a major peace accord in 1993, which envisioned the gradual implementation of Palestinian self-government in the West Bank and Gaza Strip. The Israeli-Palestinian peace process moved slowly, however, and in 2000 major fighting between Israelis and Palestinians resumed in Israel and the occupied territories.
Israel: Interesting Facts

From the CIA World Factbook and the Information Regarding Israel’s Security (IRIS) official website

Population (July 2010 est.)
7,353,985
Country comparison to the world: 96th most populated country

Area
As the comparison map to the right shows, the land currently controlled by the State of Israel (including disputed territories) is not much larger than New Jersey, which is the 5th-smallest US state. Prior to the 1967 war, Israel was 8,019 square miles or 20,770 square kilometers, just barely bigger than New Jersey.

Photo courtesy of The University of Texas at Austin

Photo courtesy of IRIS
Natural Resources
Timber, potash, copper ore, natural gas, phosphate rock, magnesium bromide, clays, sand

Literacy (2004 est.)
Definition: age 15 and over can read and write
Total population: 97.1
Male: 98.5%
Female: 95.9%

Religion (2004 est.)
Jewish 76.4%, Muslim 16%, Arab Christians 1.7%, other Christian 0.4%, Druze 1.6%, unspecified 3.9%

Natural Hazards
Sandstorms may occur during spring and summer; droughts; periodic earthquakes

Life Expectancy (2010 est.)
Total population: 80.86 years
Male: 78.7 years
Female: 83.12 years

Languages
Hebrew (official), Arabic used officially for Arab minority, English most commonly used foreign language

Capital
Name: Jerusalem
Time difference: 7 hours ahead of Charlotte during Standard Time

Executive Branch
Chief of state: President Shimon Peres (since 15 July 2007)
Head of government: Prime Minister Binyamin Netanyahu (since 31 March 2009)
Cabinet: Cabinet selected by prime minister and approved by the Knesset (Parliament)
Elections: president largely a ceremonial role and is elected by the Knesset for a seven-year term (one-term limit); election last held 13 June 2007 (next to be held in 2014 but can be called earlier); following legislative elections, the president, in consultation with party leaders, assigns the task of forming a governing coalition to a Knesset member who he or she determines is most likely to accomplish that task

Flag Description
White with a blue hexagram (six-pointed linear star) known as the Magen David (Shield of David) centered between two equal horizontal blue bands near the top and bottom edges of the flag; the basic design resembles a Jewish prayer shawl (tallit), which is white with blue stripes; the hexagram as a Jewish symbol dates back to medieval times
History of Judaism

From BBC – Religion & Ethics

The Old Testament
The history of Judaism is inseparable from the history of Jews themselves. The early part of the story is told in the Hebrew Bible (Old Testament). It describes how God chose the Jews to be an example to the world, and how God and his chosen people worked out their relationship.

The Bronze Age
Jewish history begins during the Bronze age in the Middle East. The birth of the Jewish people and the start of Judaism is told in the first 5 books of the Bible. God chose Abraham to be the father of a people who would be special to God, and who would be an example of good behaviour and holiness to the rest of the world. God guided the Jewish people through many troubles, and at the time of Moses he gave them a set of rules by which they should live, including the Ten Commandments.

The birth of Judaism
This was the beginning of Judaism as a structured religion. The Jews, under God’s guidance became a powerful people with kings such as Saul, David, and Solomon, who built the first great temple. From then on Jewish worship was focussed on the Temple, as it contained the Ark of the Covenant, and was the only place where certain rites could be carried out.

The kingdom declines
Around 920 BCE, the kingdom fell apart, and the Jewish people split into groups. This was the time of the prophets. Around 600 BCE the temple was destroyed, and the Jewish leadership was killed. Many Jews were sent into exile in Babylon. Although the Jews were soon allowed to return home, many stayed in exile, beginning the Jewish tradition of the Diaspora - living away from Israel.

Rebuilding a Jewish kingdom
The Jews grew in strength throughout the next 300 years BCE, despite their lands being ruled by foreign powers. At the same time they became more able to practice their faith freely, led by scribes and teachers who explained and interpreted the Bible. In 175 BCE the King of Syria desecrated the temple and implemented a series of laws aiming to wipe out Judaism in favour of Zeus worship. There was a revolt (164 BCE) and the temple was restored. The revolt is celebrated in the Jewish festival of Hannukah.

Roman Times
For a period the Jewish people governed themselves again and were at peace with the Roman Empire. But internal divisions weakened the Jewish kingdom and allowed the Romans to establish control in 63 BCE. In the years that followed, the Jewish people were taxed and oppressed by a series of "puppet" rulers who neglected the practice of Judaism. The priests or Sadducees were allied to the rulers and lost favour with the people, who turned increasingly to the Pharisees or Scribes. These were also known as Rabbis, meaning teachers.
Year 1: CE
What is nowadays called the 'Current Era' traditionally begins with the birth of a Jewish teacher called Jesus. His followers came to believe he was the promised Messiah and later split away from Judaism to found Christianity, a faith whose roots are firmly in Judaism.

1 CE - 70 CE: Rabbinic Judaism
The Rabbis encouraged the Jewish people to observe ethical laws in all aspects of life, and observe a cycle of prayer and festivals in the home and at synagogues. This involved a major rethink of Jewish life. Although the Temple still stood, its unique place as the focus of Jewish prayer and practice was diminished. Many synagogues had been founded in Palestine and right around the Jewish Diaspora. Great teaching academies were founded in the first century BCE with scholars discussing and debating God's laws. The most well known of the early teachers were Hillel, and his contemporary Shammai.

70 - 200 CE: The destruction of the Temple
This was a period of great change - political, religious, cultural and social turmoil abounded in Palestine. The Jewish academies flourished but many Jews could not bear being ruled over by the Romans. During the first 150 years CE the Jews twice rebelled against their Roman leaders, both rebellions were brutally put down, and were followed by stern restrictions on Jewish freedom. The first revolt, in 70 CE, led to the destruction of the Temple. This brought to an end the temple worship and is still perceived by traditional Jews as the biggest trauma in Jewish history. It is marked by the fast day of Tisha B'Av (meaning the ninth day of the month of Av). A second revolt, in 132 CE, resulted in the death of hundreds of thousands of Jews, the enslaving of thousands of others, and the banning of Jews from Jerusalem.

200 - 700 CE: The Mishna and Talmud
Between 200 and 700 CE Judaism developed rapidly. Following the twin religious and political traumas, the academies moved to new centres both in Palestine and in the Diaspora. A sense of urgency had taken hold and it was considered vital to write down the teachings of the Rabbis so that Judaism could continue. Around 200 CE, scholars compiled the Mishna, the collection of teachings, sayings and interpretations of the early Rabbis. The academies continued their work and several generations of Rabbis followed. Their teachings were compiled in the Talmud which expands on the interpretations of the Mishna and established an all-encompassing guide to life. The Talmud exists in two forms. The first was finalised around the 3rd century CE in Palestine, and the second and superior version was completed during the 5th century CE in Babylon. During this period Jews were allowed to become Roman citizens, but later were forbidden to own Christian slaves or to marry Christians. In 439 CE the Romans banned synagogue building, and barred Jews from official jobs.

The Golden Age — The Jews in Spain
The years either side of 1000 CE were the golden age of the Jews in Spain. Co-existing happily with the country’s Islamic rulers the Jews developed a flourishing study of Science, Hebrew literature and the Talmud. Despite an attempt to forcibly convert all Jews to Islam in 1086 CE, this golden age continued. At around this time the first Jews are recorded in Britain.
The Crusades
The next Millennium began with the Crusades, military operations by Christian countries to capture the Holy Land. The armies of the first Crusade attacked Jewish communities on their way to Palestine, especially in Germany. When the Crusaders captured Jerusalem they slaughtered and enslaved thousands of Jews as well as Muslims. Following the example of the Romans earlier, they banned Jews from the city. In Britain, the Jewish population increased, benefiting from the protection of Henry I.

The bad times return
The 1100s were a bad period for the Jews. Jews were driven from southern Spain by a Berber invasion. Serious anti-Jewish incidents began to occur in Europe:
- in France Jews were accused of ritually murdering a child
- in England Jews were murdered while trying to give gifts to the King at Richard I’s coronation
- 150 Jews were massacred in York
- in 1215 the Catholic Church ordered Jews to live in segregated areas (ghettos) and to wear distinctive clothes.

Expulsions
In England the Jews faced increasing restrictions during the Thirteenth Century, and in 1290 they were all expelled from England. Shortly afterwards the Jews were expelled from France. In 1478 the Jews in Spain suffered under the Spanish Inquisition, and in 1492 Jews were expelled from Spain altogether. The same thing happened in Portugal in 1497. 50 years later in Germany, Martin Luther (founder of Protestant Christianity) preached viciously against the Jews.

Scholarship, literature, and mysticism
Certain parts of Jewish culture continued to thrive, despite this tough time. Scholarship and literature flourished, with figures like Rambam, Luria, Levi ben Gershom, and Eleazar ben Judah. The Jewish form of mysticism, known as Kabbalah reached new heights with the publication in Spain of the Book of Splendour, which influenced Jewish Spirituality for centuries.

Jews return to Britain
This was a period of Jewish expansion. Jews were allowed to return to England and their rights of citizenship steadily increased. In 1760 the main representative organisation for British Jewry, The Board of Deputies of British Jews, was founded. Jews were first recorded in America in 1648.

Hassidism
Poland and Central Europe saw the creation of a new Jewish movement of immense importance - Hassidism. It followed the example of the Baal Shem Tov (1700-1760) who said that you didn’t have to be an ascetic to be holy; indeed he thought that the appropriate mood for worship was one of joy. The movement included large amounts of Kabbalistic mysticism as well, and the way it made holiness in every day life both intelligible and enjoyable, helped it achieve great popularity among ordinary Jews. However it also led to divisions within
Judaism, as many in the religious establishment were strongly against it. In Lithuania in 1772 Hassidism was excommunicated, and Hassidic Jews were banned from marrying or doing business with other Jews.

**Persecution in Central Europe**
Towards the end of the 1700s Jews began to suffer persecution in central Europe, and in Russia they began to be restricted to living in a particular area of the country, called The Pale.

**The birth of Reform Judaism**
In the 19th Century another new movement appeared in Judaism. This was Reform Judaism, which began in Germany and held that Jewish law and ritual should move with the times, and not be fixed. It introduced many changes to worship, and customs, and grew rapidly into a strong movement. It continues to flourish in Europe and the USA.

**Good news and bad news**
As the 19th century continued many countries gradually withdrew restrictions on Jews—the UK allowed its Jewish citizens the same rights as others by 1860s. But at the same time Jews came under increasing pressure in central Europe and Russia. There were brutal pogroms against Jews in which they were ejected from their homes and villages, and cruelly treated. Some of this persecution is told in the musical show Fiddler on the Roof. In Israel, Jewish culture was having a significant rebirth as the Hebrew language was recreated from a language of history and religion into a language of everyday life.

**UK and USA**
In Britain and America this was the century of Jewish immigration, with great numbers of Jewish people arriving to escape the pogroms in Poland and Russia. The Jewish population of Britain increased by 250,000 in 30 years. It was at this time that the East End of London became a centre of Jewish life in Britain. However in 1905 the UK passed a law that slowed immigration to a mere trickle.

**The birth of Zionism**
The Zionist movement, whose aim was to create a Jewish state, was rooted in centuries of Jewish prayer and yearning to return to the land of Israel. Political Zionism began in the mid-19th Century and towards the end of the century it gained strength as many Jews began to feel that the only way they could live in safety would be to have a country of their own. In 1917, in the Balfour Declaration, the UK agreed that a Jewish state should be established in Israel and, following the First World War, the British governed the region in preparation for a permanent political arrangement. Over the next few years Jewish immigration increased and important institutions were founded such as the Israeli Chief Rabbinate, and the Hebrew University.

**The Holocaust**
Jewish history of the 1930s and 1940s is dominated by the Holocaust, the implementation on an industrial scale of a plan to wipe the whole Jewish people from the face of Europe. The plan was carried out by the Nazi government of Germany and their allies. During the Holocaust 6 million Jewish people were murdered, 1 million of them children. The events of
the Holocaust have shaped Jewish thinking, and the thinking of other people about Jewish issues ever since. War crimes trials of those involved in the Holocaust continue to this day. The tragedy affected much of the religious thinking of Jews, as they try to make sense of a God who could allow such a thing to happen to his chosen people.

**The State of Israel**
The second defining Jewish event of the century was the achievement of the Zionist movement in the creation of the State of Israel in 1948. There had been strong and paramilitary opposition to British colonial rule for many years, and in 1947 the United Nations agreed a plan to partition the land between Jews and Arabs. In May 1948 the British Government withdrew their forces. Immediately, the surrounding Arab States invaded and the new Jewish State was forced to fight the first of several major wars. Notable among these were the 6-day war in 1967 and the Yom Kippur war in 1973. The first steps towards a permanent peace came when Israel signed a peace treaty with Egypt in 1979, and with Jordan in 1994. For most of its history Israel has had an uneasy relationship with the Arab states that surround it, and has been greatly sustained by the help and support of the USA, where the Jewish community is large and influential. The 21st century began with great political uncertainty over Israel and its relationship with the Palestinian people, and this continues.
What is Judaism?

By Tracy R. Rich

www.jewfaq.org

What is Judaism? What does it mean to be a Jew? Most people, both Jewish and gentile, would instinctively say that Judaism is a religion. And yet, there are militant atheists who insist that they are Jews! Is Judaism a race? If you were to say so, most Jews would think you were an antisemite! So what is Judaism?

Is Judaism a Religion?

Clearly, there is a religion called Judaism, a set of ideas about the world and the way we should live our lives that is called "Judaism." It is studied in Religious Studies courses and taught to Jewish children in Hebrew schools. There is a lot of flexibility about certain aspects of those beliefs, and a lot of disagreement about specifics, but that flexibility is built into the organized system of belief that is Judaism.

However, many people who call themselves Jews do not believe in that religion at all! More than half of all Jews in Israel today call themselves "secular," and don't believe in G-d or any of the religious beliefs of Judaism. Half of all Jews in the United States don't belong to any synagogue. They may practice some of the rituals of Judaism and celebrate some of the holidays, but they don't think of these actions as religious activities. The most traditional Jews and the most liberal Jews and everyone in between would agree that these secular people are still Jews, regardless of their disbelief. Clearly, then, there is more to being Jewish than just a religion.

Are Jews a Race?

In the 1980s, the United States Supreme Court ruled that Jews are a race, at least for purposes of certain anti-discrimination laws. Their reasoning: at the time these laws were passed, people routinely spoke of the "Jewish race" or the "Italian race" as well as the "Negro race," so that is what the legislators intended to protect.

But many Jews were deeply offended by that decision, offended by any hint that Jews could be considered a race. The idea of Jews as a race brings to mind nightmarish visions of Nazi Germany, where Jews were declared to be not just a race, but an inferior race that had to be rounded up into ghettos and exterminated like vermin. But setting aside the emotional issues, Jews are clearly not a race.

Race is a genetic distinction, and refers to people with shared ancestry and shared genetic traits. You can't change your race; it's in your DNA. I could never become black or Asian no matter how much I might want to.
Common ancestry is not required to be a Jew. Many Jews worldwide share common ancestry, as shown by genetic research; however, you can be a Jew without sharing this common ancestry, for example, by converting. Thus, although I could never become black or Asian, blacks and Asians have become Jews (Sammy Davis Jr. and Connie Chung).

Is It a Culture or Ethnic Group?

Most secular American Jews think of their Jewishness as a matter of culture or ethnicity. When they think of Jewish culture, they think of the food, of the Yiddish language, of some limited holiday observances, and of cultural values like the emphasis on education.

Those secular American Jews would probably be surprised to learn that much of what they think of as Jewish culture is really just Ashkenazic Jewish culture, the culture of Jews whose ancestors come from one part of the world. Jews have lived in many parts of the world and have developed many different traditions. As a Sephardic friend likes to remind me, Yiddish is not part of his culture, nor are bagels and lox, chopped liver, latkes, gefilte fish or matzah ball soup. His idea of Jewish cooking includes bourekas, phyllo dough pastries filled with cheese or spinach. His ancestors probably wouldn't know what to do with a dreidel.

There are certainly cultural traits and behaviors that are shared by many Jews that make us feel more comfortable with other Jews. Jews in many parts of the world share many of those cultural aspects. However, that culture is not shared by all Jews all over the world, and people who do not share that culture are no less Jews because of it. Thus, Judaism must be something more than a culture or an ethnic group.

Are the Jews a Nation?

The traditional explanation, and the one given in the Torah, is that the Jews are a nation. The Hebrew word, believe it or not, is "goy." The Torah and the rabbis used this term not in the modern sense meaning a territorial and political entity, but in the ancient sense meaning a group of people with a common history, a common destiny, and a sense that we are all connected to each other.

Unfortunately, in modern times, the term "nation" has become too contaminated by ugly, jingoistic notions of a country obsessed with its own superiority and bent on world domination. Because of this notion of "nationhood," Jews are often falsely accused of being disloyal to their own country in favor of their loyalty to the Jewish "nation," of being more loyal to Israel than to their home country. Some have gone so far as to use this distorted interpretation of "nationhood" to prove that Jews do, or seek to, control the world. In fact, a surprising number of antisemitic
websites and newsgroup postings linked to this page (in an earlier form) as proof of their antisemitic delusions that Jews are nationalistic, that Israel is a colonial power and so forth. Because of the inaccurate connotations that have attached themselves to the term "nation," the term can no longer be used to accurately describe the Jewish people.

The Jewish People are a Family

It is clear from the discussion above that there is a certain amount of truth in the claims that it is a religion, a race, or an ethnic group, none of these descriptions is entirely adequate to describe what connects Jews to other Jews. And yet, almost all Jews feel a sense of connectedness to each other that many find hard to explain, define, or even understand. Traditionally, this interconnectedness was understood as "nationhood" or "peoplehood," but those terms have become so distorted over time that they are no longer accurate.

Rabbi Adin Steinsaltz has suggested a better analogy for the Jewish people: We are a family. See the third essay in his recent book, We Jews: Who Are We and What Should We Do. But though this is a new book, it is certainly not a new concept: throughout the Bible and Jewish literature, the Jewish people are referred to as "the Children of Israel," a reference to the fact that we are all the physical or spiritual descendants of the Patriarch Jacob, who was later called Israel. In other words, we are part of his extended family…
What is a Cantor?

The following text is a transcription of a video by Jeremiah Lockwood at myjewishlearning.com. It was transcribed by Kitengie Milka Shisso of The Echo Foundation.

Hazzanut, or cantorial music, is the spiritual music tradition of the Jewish people. Hazzan, or cantor, is the title of the singer who leads the prayers in the synagogues. The cantor must be both a repository of traditional music and a powerful galvanizing force for the communal expression of religious feeling. Cantorial music is based on a system of musical modes called nusah. There is a different nusah for each of the three prayer services each day, as well as for the Sabbath and all of the holidays that mark the Jewish calendar. A great cantor must be a master of the entire system of nusah and have the ability to improvise within each of the different modes in order to bring out the rich emotional content of the prayer poetry being sung.

Many of the great cantors of the past were also wonderful composers whose work blurred the boundary between religious and aesthetic achievement. In the greatest cantors, one can perceive a stunning combination of humility and triumphant spiritual strengths. And although in the present day the role of the cantor has diminished in synagogue life, one can still perceive in the historical figure of cantorial music, a role model for creative work in the present day.

Cantorial Music Samples

Yossele Rosenblatt’s “Shir Hama’ a lot”
http://www.chazzanut.com/rosenblatt/rosenblatt-shir-hama%27alot.mp3

Gershon Sirota’s “Veshamru” “Reitzei”
http://www.youtube.com/watch?v=3KXrgCZ5Ars

Mordechai Hershman “Eilu Devarim”
http://www.youtube.com/watch?v=cnc59rdf4pY&feature=related

Zavel Kwartin’s “Tipher Rabbi Yishma’el”
http://www.youtube.com/watch?v=X4m2mdu5jjU

Moshe Koussevitzky’s “Esa Einai”
http://www.youtube.com/watch?v=TQlpsZzuxgo

Joseph Malovany “Maariv”
http://www.youtube.com/watch?v=m0POUCHAAto&feature=related

More cantorial music downloads
http://chazzanut.org/download/libsonmo/
21st Century Cantor: Joseph Malovany

From www.5as.org, the official website for the Fifth Avenue Synagogue, where Cantor Malovany has served as cantor since 1973.

Joseph Malovany possesses a brilliant spinto tenor voice, described by the London Guardian as "most powerful, beautiful and expressive spinto technique...sturdy and heroic" and by the Swedish newspaper Goteborgs Posten as "Judaism's Jussi Bjorling".

Leonard Bernstein, after hearing him over the Jewish High Holy Days, expressed his hope to hear Cantor Malovany "sing beyond the Altar." Although he turned down invitations to sing major operatic rolls on the opera stage, Joseph Malovany does perform oratorias and symphonic works which require the tenor voice as the soloist.

Dedication to World Jewry
For many years, Joseph Malovany has sung the holocaust memorial prayers at the central New York commemorations at Madison Square Garden, attended by the President and the Vice President of the United States and the Prime Minister of Israel. His heartfelt memorial prayer was chanted at the memorial service for Prime Minister Yitzhak Rabin at the Carnegie Hall in New York.

In January 1998 he was the soloist in Philadelphia at the American premiere of this symphony with the combined orchestra consisting of the Israel Philharmonic Orchestra and The Philadelphia Orchestra under the baton of Maestro Zubin Mehta. Over 20,000 people attended this event which officially opened the American year-long celebrations commemorating Israel's Fiftieth Anniversary.

Education
He currently holds the academic position of Distinguished Professor of Liturgical Music at Yeshiva University. He also holds the position of Dean of the J.D.C. Moscow Academy of Jewish Music. Born in Tel-Aviv, Israel, he served as Cantor at Tel-Aviv's Bilu synagogue, as Cantor of the Israeli Army and at synagogues in Johannesburg, South Africa and London, England. Joseph Malovany is a holder of the highest artistic diplomas from the Music Academy in Tel Aviv and from Great Britain's Royal Academy and Trinity College of Music. He has been awarded the "Fellow" of the Trinity College of Music as well as many citations and honors from various national and international organizations. He is Honorary President of the Cantorial Council of America and Past Chairman of the Board of the American Society for Jewish Music.

Photo courtesy of Festival of Jewish Culture
In 1997, he was awarded the Joseph Malovany Chair for Advanced Studies in Jewish Liturgical Music at the Belz School of Music Yeshiva University.

Touring The World
[Joseph Malovany] has toured extensively in Europe, South America and in the United States with many international orchestras including the Israel Philharmonic, the Russian State Symphony, the Belgium Radio Symphony, the Mexico Symphony, the London Classical, the New York Symphony, he Bucharest Opera Orchestra, the Lithuanian National Symphony Orchestra the Hungarian State Orchestra and the Romanian Radio and Television Orchestras, among many others.

He has appeared at Amsterdam's Royal Opera House, London's Royal Festival and Queen Elizabeth Halls and Barbican Center, Lincoln Center's Avery Fisher and Alice Tully Halls in New York, the Core States Center in Philadelphia and Brussels Palace of Fine Arts. Joseph Malovany has concertized extensively with performances at Sao Paulo's Teatro Cultura Artistica, the Harodion Amphitheater near Bethlehem and in Toledo and the opera house of Santander, Spain.

Cantor Malovany recently received the honor of being knighted as "Commander of the Legion of Honor" by President Aleksander Kwasniewski of the Republic of Poland.
Judaica Artifacts

http://www.aam-us.org/museumresources/prov/procedures.cfm

The term "Judaica" is most broadly defined as the material culture of the Jewish people. First and foremost this includes ceremonial objects for communal or domestic use. In addition, Judaica comprises historical artifacts relating to important Jewish personalities, momentous events, and significant communal activities, as well as literature relating to Jews and Judaism. Many museums also have acquired material of everyday life that expresses a uniquely Jewish identity.

The Mezuzah
From Jewish Virtual Library

On the doorposts of traditional Jewish homes (and many not-so-traditional homes!), you will find a small case like the one pictured at right. This case is commonly known as a mezuzah (Hebrew: doorpost), because it is placed upon the doorposts of the house. The mezuzah is not, as some suppose, a good-luck charm, nor does it have any connection with the lamb's blood placed on the doorposts in Egypt. Rather, it is a constant reminder of God's presence and God's commandments.

The commandment to place mezuzot (mezuzah) on the doorposts of Jewish houses is derived from Deuteronomy 6:4-9, a passage commonly known as the Shema. In that passage, God commands Jews to keep His words constantly in their minds and in their hearts by (among other things) writing them on the doorposts of their houses. The words of the Shema are written on a tiny scroll of parchment, along with the words of a companion passage, Deuteronomy 11:13. On the back of the scroll, a name of God is written. The scroll is then rolled up and placed in the case, so that the first letter of the Name (the letter Shin) is visible (or, more commonly, the letter Shin is written on the outside of the case).

Torah Pointer
From Canada Virtual Museum

The reader of the Torah uses a pointer in order to follow the lines of the text since it is forbidden to touch the parchment directly. All pointers are decorated with a hand and pointed index finger. The Hebrew name given to the pointer, yad, literally means "hand." The five fingers represented at the end of the pointer also refer to the five books of the Torah.
Kiddush Cup
From Canada Virtual Museum

In order to be used for the Kiddush over the wine on the eve of Shabbat, a cup cannot show any sign of damage. Silver, a very durable metal, is therefore commonly used to make Kiddush Cups. This cup is decorated with designs of grapes and foliage. The grapes relate to the content of the cup, the wine, but are also a symbol of the land of Israel. Grapes are one of the seven sacred fruits that are native to the region. A Hebrew inscription appears on the bowl of the cup: "There is no joy unless it is with wine. It will gladden your heart."

Shabbat Candlesticks
From Canada Virtual Museum

These silver Shabbat candlesticks were made in Vienna in the mid-nineteenth century. They are of traditional form, consisting of two decorated shafts in silver. At least two candles are lit as a reminder of the double command in the Bible to both remember and observe Shabbat. The two candles also symbolize the belief that celebrating Shabbat grants every individual a second soul. In some households, more than two candles are lit. The additional candles may represent each member of the family, but a minimum of two Shabbat lights is always present. Traditionally, the women in the household light the Shabbat Candles and say a blessing.

Shabbat Hanging Lamp
From Canada Virtual Museum

This lamp is typical of German Shabbat lamps, which evolved from an old type of star-shaped domestic oil lamp used in medieval Europe by both Jews and non-Jews. In Jewish homes, the lamp was lit at the start of Shabbat to provide light over the holiday. The lamp developed into a ritual object when this purpose became obsolete. Around the sixteenth century, this form of lamp became known by its German name *Judenstern*, or Jewish Star.
**Megillat Esther Scroll**
From My Jewish Learning

The Scroll of Esther, known as the Megillah, is chanted in the synagogue on the eve of Purim and again the next morning. Megillat Esther tells the story of the salvation of the Jews of the Persian Empire. The Scroll of Esther is universally known as the Megillah, not because it is the most important of the five scrolls, but due to its immense popularity, the prominence that is given to its public reading, and the fact that it is the only one that is still generally read from a parchment scroll. At one time, it was normative for every Jewish household to possess a Megillah, and much time and skill were devoted to the production of beautifully illuminated texts and elaborate wooden and silver cases that would house the scroll.

**Darmstadt Haggadah**
From Canada Virtual Museum

The Haggadah, literally translated as "telling," recounts the story of Passover. The Darmstadt Haggadah is one of the most famous and oldest known Haggadahs. It was written and illuminated in 1430 by the scribe Israel Ben Meir of Heidelberg, Germany. In the 1700s, Baron Hupsch bought the Darmstadt Haggadah and put it in storage in Cologne, Germany, where it stayed for two hundred years. In 1928, it was reproduced by Germany's Aron Publishers. The example that you see here was printed at that time.

It was assumed that the original was destroyed during the Holocaust, but it was later discovered at the Museum of Leatherwork in Offenbach, Germany. The Nazis had the manuscript on display in 1941 to show off its fifteenth-century leather binding, not revealing that the interior held Hebrew script. Unlike the pages of other Jewish texts, such as the Torah or prayer books, the Haggadah is often richly decorated.
**Seder Plate**
From Canada Virtual Museum

The Seder plate is placed on the table during the Passover meal. Foods that are symbolic of the Passover story are placed on the plate. For example, bitter herbs are reminiscent of the suffering of the Jews in Egypt. Charoset, which is a mixture of apples, wine, walnuts and cinnamon, is visually reminiscent of the mortar used by the Jews to lay bricks when they were slaves. Salt water symbolizes the tears of their ancestors, and an egg is a sign of the continuing circle of life.

**Chanukah Lamp**
From Canada Virtual Museum

This standing Chanukah lamp is a smaller version of the candelabrum that was lit in synagogues for the sake of wayfarers and tourists who could not kindle the lights at home. In the 1800s in Germany, the standing lamp began to be produced on a smaller scale for domestic use.

**Shofar**
From Canada Virtual Museum

The Shofar is sounded during the Jewish High Holidays. The sound of the Shofar is intended to awaken the conscience of every Jew and call him or her to prayer and repentance. It also commemorates the destruction of the Temple by reminding us of the trumpets of the enemy army. The Shofar is usually made of a ram's horn and is most often left undecorated.

Rosh Hashanah means 'the head of the year,' or New Year. The holiday of Rosh Hashanah marks the beginning of the Ten Days of Penitence, when Jews ask for forgiveness for their sins. Blowing the Shofar announces the beginning of the ten-day period. Yom Kippur, or the Day of Atonement, is the culmination of the Ten Days of Penitence. It is the most solemn and important holiday in the Jewish year, and is characterized by fasting and prayer. The final service of Yom Kippur ends with the blowing of the Shofar.
Menorah
From Jewish Virtual Library

One of the oldest symbols of the Jewish faith is the menorah, a seven-branched candelabrum used in the Temple, which is lit every evening. The menorah in the First and Second Temples had seven branches. After the Temples were destroyed, a tradition developed not to duplicate anything from the Temple and therefore menorahs no longer had seven branches. The use of six-branched menorahs became popular, but, in modern times, some rabbis have gone back to the seven-branched menorahs, arguing that they are not the same as those used in the Temple because today's are electrified.

The nine-branched menorah used on Chanukah is commonly patterned after this menorah, because Chanukah commemorates the miracle that a day's worth of oil for this menorah lasted eight days.

Dreidel
From Canada Virtual Museum

During the eight nights of Chanukah, children receive gifts and play the game of dreidel. The dreidel is a spinning top with four sides. Each side of the dreidel is decorated with a Hebrew letter: a nun, gimel, hei, or shin. These letters stand for the Hebrew phrase nes gadol hayah sham, meaning “a great miracle happened there.” On dreidels made in Israel, one letter is different. The shin is replaced by a pei so that the letters indicate that “a great miracle happened here.” In addition to reminding us of the miracle of Chanukah, the letters on the dreidel also represent how much a player has won or lost while playing the game of dreidel. At the start of the game, each player puts some coins into a pot. When a player spins a nun, he or she gets nothing. A gimel wins the whole pot, a hei wins half the pot, and a shin means that the player must put more coins into the pot.
Chapter Study Questions

1. Do you think Jews are entitled to have their own state? Why or why not?

2. Why did the location of the Jewish state matter to Theodor Herzl and others?

3. In your opinion, did the United Nations have the right to establish a Jewish state in Israel without the Arabs’ consent? Did the Arabs have a right to disagree with this decision?

4. Create a timeline of the major events in the history of Judaism. Why did you choose to include those particular events? If a group of conservative Jews, secular Jews, and non-Jews were to do this exercise, how do you think the timelines would differ for each?

5. Define the Zionist movement. What were the objectives of the movement? Was it successful?

6. Do you think of Judaism as a culture, race, ethnic group, religion, or a mixture of two or more of these? Explain your reasoning.

7. Describe your first reaction when you listened to the cantorial music samples listed on page 38. Was this your first time to listen to this type of music? Was it enjoyable? Why or why not?

8. In your own opinion, what is the significance of Judaica artifacts to the Jewish community? Do you have any artifacts in your own culture with similar significance?
III. Social Interests

“Prof. Ciechanover does not confine himself to an ivory tower, and has expressed his opinion on a range of pressing public issues. He serves as a prominent figure warning of the erosion in the status of education, science, culture, and intellectual life in Israel, and has called for a change in national priorities in order to save the education and higher education systems from collapse. He argues that ‘the strength of Israel and its international standing depend on extensive investments in the various sciences as well as in the study of Judaism and the history of the Land of Israel.’”

Excerpt taken from Dr. Ciechanover’s biography on the Lorry I. Lokey Center official website

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“At home, I grew up on books. I was embedded into the atmosphere of studying…I don’t know what my father wanted me to be…but he wanted me to be a citizen of the world, understanding languages, math, open to accept and to absorb everything…”

-- Dr. Ciechanover, excerpted from a 2006 video interview with the Vega Science Trust

**The Education System of Israel**

By Tara Schumacher

[http://handouts.aacrao.org/am08/finished/T1100a_T_Schumacher.pdf](http://handouts.aacrao.org/am08/finished/T1100a_T_Schumacher.pdf)

2008

**Educational Overview**

Israeli schools today may be classified in general either as a state school, a state-religious school, an Agudat Yisrael school or an Arab school (Christian, Druze or Islamic). A separate educational structure is maintained for Arab students, though some Arabs study in the Jewish system. The language of instruction in Jewish Schools is Hebrew and in the Arab schools is Arabic. Higher education is under the control of the Council for Higher Education. The Council has the power to recognize institutions of higher education and to grant authority to award degrees. Although no accreditation system operates in Israel as in the United States, the Council serves a similar purpose.

**Primary Education**

All primary schools offered eight-year programs prior to 1975. Post-1975 reforms made primary school six years and post-primary six years, split between junior or intermediate school and high school. The basic curriculum in Jewish and Arab schools is relatively the same. Foreign languages in Hebrew schools will either be in English or French. Foreign language training begins in sixth grade. In Arab schools all students begin to study Hebrew in third grade. A second foreign language such as English or French may be added in the sixth grade. Religious studies are required in all types of school.

**Secondary Education**

Secondary education in Israel is based on European models, largely because of the influx of Eastern Europeans after World War II and Great Britain's earlier occupation of Palestine. The years of secondary education find students categorized into academic and vocational tracks. The last three years (grades ten through twelve) are neither compulsory nor free. In academic schools, students take general courses and then specialize during their last two years. In vocational schools students engage in technical, maritime, domestic or business studies.
Higher Education
Higher education in Israel is designated as either post-secondary or higher education. Higher education is offered by three types of institutions: non-university institutions of higher education offering instruction in fields of technology, the arts, and teaching training; regional colleges; and universities.

There are eight universities in Israel, all autonomous institutions but are recognized by the Council for Higher Education. Universities are governed by their own boards of governors and the Ministry and Council are not directly involved in running these institutions. Israeli degrees present no special problems for United States admission officers because the nomenclature is similar, with one exception: professional degrees are first degrees in Israel, not second degrees (e.g., the LLB in Israel and the JD in the U.S.) The basic first degrees are the BA and the BSc, followed by the MA, the MSc and the PhD. Credentials are issued in English by Israeli universities, especially if the student is applying to a U.S. university.

Post-Secondary Technical Education
Training for technical professions usually encompasses engineering and technology fields. These technical fields usually supplement the trained graduates of university faculties of engineering and technology. This credential is similar to technical and vocational programs offered at U.S. junior/community colleges. These programs are offered at specialized technical and vocational colleges. Technical degrees awarded after the first year of education are the qualification for a “technician.” This degree is usually considered comparable to one year of U.S. university study. The Handassai degree is awarded after two years of engineering education and the qualification is that of a “practical engineer.” This degree is usually considered comparable to two years of U.S. university study.

Technion students on the lawn. Photo courtesy of the Technion.
## Israel Educational System - New System (Since 1975)

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### Entrance Exams

**Compulsory Military - Israel Defence Forces (IDF)**

- Age: 20-22 (Women); 21-23 (Men)
- **Take Bagrut, go to Vocational, or enter IDF**

### Bagrut Academic Secondary School Leaving Examinations

**IDF**

- Israeli Defense Forces (2 years compulsory for women, 3 years compulsory for men): entered upon completion of secondary school, before entrance into University, or after completion of certain post-secondary vocational/technical programs which warrant a deferment, or entered after secondary school either before entering vocational/technical programs or before passing the Bagrut examination and entering a university.

**Exams**

- Examinations designed by the individual university faculties

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## Vocational Technical 2-3 years

## Schools for Working Youth (4 years)

### Ages 14-17

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### University (3 years)

- Age: 20-22 (Women); 21-23 (Men)

### Master’s Degree (2 years)

### Doctorate (2-3 years)
The United States Education System

From the Swiss Federal Department of Foreign Affairs
Talk with Nobel Prize Winner, Dr. Ciechanover

On the Significance of Creating Ideas and Judgments from Individual Creativity and Initiative Plus a Conclusion on what is Important

Kyudai News: Kyushu University Campus Magazine
February 22, 2005

MC: Today we are very honoured and privileged to welcome you, Dr. Aaron Ciechanover (hereafter Dr. Ciechanover), to Kyushu University, after you were awarded the Nobel Prize for chemistry in 2004. Taking advantage of this good opportunity, we arranged this interview session with President Kajiyama and Professor Fujiki, who have invited you to our campus today. We here today are all looking forward to hearing what inspiring words such distinguished scientists as yourselves will have for students of universities and high schools as well as young researchers…

Dr. Ciechanover: …As a guest in Japan, I admire this country for many good reasons. If fact, I shall be doing my second sabbatical here, when I come here again next year. Israel, however, somehow chose a different system in order to run its science. Maybe it is because Israel is young. We are not bound to any tradition. We have a long history, but as a modern country we are still in infancy, at only 57 years old. When we established our university about 60, 70, or 80 years ago, we decided to adopt the American system. For better or worse, the American system says that everybody is independent. In that system, you bring in a young professor, give him a bench and some money, and tell him to go to work on his ideas. He is not working for anybody. He is working only for himself. In six or seven years, he is up for tenure, a permanent position. He is being judged only by his achievement. His imagination and his ability also occur independently through his science.

Professor Fujiki: …Yes, I also have the experience of studying in the United States for ten years under such a system, which I greatly admired. It gives competitiveness and credit to those who have ability. Such a vitalizing system seems to be working well in the United States to develop it as a strong multi-national country. But I think there are two sides here, as you said. Traditional and cultural factors in Japan also sometimes have good aspects. However, I want the young people of Japan to be more aggressive. I think this is also your message to the young students in Japan.
President: I also agree with you, Dr. Ciechanover, since I also have the experience of studying in the United States. I think this system has been successful for about 95% of the time. The question is how about the remaining 5%. Science sometimes requires group work…

It has been about 100 years since national universities were established in Japan. At the time of their introduction, we introduced the German system, which is the chair system. While it has both good and bad points, Kyushu University is still run basically under this chair system. As the president of the university, I regret to tell you that we have started to notice some of the adverse effects of this system. It is difficult to change the system. Therefore, I had to think about alternative ways of encouraging individual researchers. Under the chair system, professors procure grants for research and allocate grants to each of their junior researchers. This, however, can spoil the researchers. Then, the researchers gradually stop obtaining grants aggressively by themselves. In this sense, I personally believe it is important for young scientists to be independent from their professors.

Dr. Ciechanover: I am fully aware of the Japanese system, maybe much more than you can imagine. I have been in this country for almost a year altogether. It does not have to copy the American system. Every country should adapt according to its own needs. In addition, you should not make a revolution overnight, because it becomes bloody. We don't want to destroy the system. It is true that for the remaining 5%, as you mentioned, our efforts have to be made in groups. The individual scientist cannot do everything by himself. He needs a group around him. In the end, however, we should not lose sight of the targets. The targets are independence and freedom of thinking. And if this is all clear, everything is clear.

Professor Fujiki: …In Japan, the government has come up with many initiatives including the promotion of education to encourage students. These are intended to educate young people to be competent not only in the field of science but also in industry. But my own impression is that recipients of this service are not reacting as actively as expected. We have grave concerns about young people just waiting for instruction to be given to them. They lack a sense of enthusiasm. They seem to regard it as more important to enjoy everyday life. As a bioscience professor I really worry about the future of Japan. Although the government has prepared many good systems to benefit students, students themselves are not responding properly. Now I am aware of our own responsibility as teachers, and we are committed to making further efforts to improve these situations. I think that the fact that Japan became an affluent country economically triggered this
tendency…I don't think this trend will be allowed to be tolerated much longer. I always try to whip up the enthusiasm of my students in the classroom, but it just seems to slip out of their heads. This is the dilemma we now face.

**President:** In addition, in terms of education in Japan, we lack the custom of encouraging children to ask questions. It is very important to encourage them to learn the joy of asking questions. I think it is also important for young people to pay more attention to the surrounding situations and changes occurring around them, and to have their own opinions about these changes. These could be changes in nature, the townscape, politics, or the economy. If they have their own opinions, it will lead to the cultivation of their own individuality, which then leads to originality and, in the end, creativity. I think Japan lacks those two points. In contrast, people in the United States have these habits. Children in America know the joy of asking questions and have their own ideas. I think that is the case in Israel, too. May I ask you whether you have these kinds of human development initiatives in Israel?

![Photo courtesy of Kyudai News](image)

**Dr Ciechanover:** Well, President Kajiyama raised two extremely important issues…

One issue has to do with general attitudes of young people. We are facing the same problem. Even Americans are facing the same problem. They lack initiative, lying back and just waiting for some miracle to happen. We are spoiled in Western civilization. The only people, I think, on earth who have not suffered yet, but may suffer in the future, are the Chinese. They will probably become the next American or next Japanese as far as the future of industries and high-tech fields are concerned. Ultimately, however, they could also suffer from this disease. Actually, the Chinese are now starting to dominate American markets. They are becoming professors and researchers, taking the places of Americans themselves in American universities.

But what can we do about this? Well, there is no magical solution except for hard work. In Israel, I am not sure how successful it is going to be, but we have decided that this problem has to do with basic education from kindergarten. In order to start such education, you also need very good teachers. And good teachers need good salaries. Because teaching in elementary schools and kindergartens has become a second grade profession, people don't want to become teachers. So it is a problem, and parents are complaining. We need to bring teachers back to their former status.
found in the world of 300 years ago: a respected profession with a high income. Then, very good people will be attracted to educating the young generation.

This is not a problem of universities alone. Universities always get the products of 12 or 15 years of education: three years of kindergarten, six years of elementary school, and six years of high school. In short, universities could do something, but they cannot do a lot. The products we are getting at universities have already had 15 years of education. If we do not change this education system, the universities will not be able to do as much as they want.

We have to convey a clear message to the young generations and their parents. At the same time, education goes hand with hand with high incomes, a high social status, and a high level of health. The more income we have, the more education we have and the healthier we should be. The more income we bring to our families, the better our situation will be. It is clear that uneducated people belong to low income layers of the population. With education, I hope this problem will be resolved. It's not just your problem, so don't worry. We are in the very same pot.

**MC:** Lastly, could you please give a message to the students of Kyushu University and young researchers?

**Dr. Ciechanover:** This is applicable not only to the students of Kyushu University, but to all students and young researchers. Be yourself. Think independently and challenge your professors. Don't take anything for granted. As you said, don't be shy, and ask interrogative questions.

**All:** Thank you very much.
We are living in a world with inherent paradoxes. Science and technology have been driving us to the outer space, to the innermost world of the human genome and personalized medicine, and to all that is in between -- the ability to communicate in an unprecedented manner, to travel to the farthest corners of the universe, and to enjoy culture in the broadest meaning of the word.

Yet, at the same time millions are still sacrificed on the altar of religious fundamentalism and political intolerance, whereas many others are living with no dignity in humiliating poverty, starving for a piece of bread, thirsty for a cup of clean water, and, needless to say, having no access to basic human needs -- education, health and social services. Even the wonderful achievements of science and technology become at times a double-edged sword. We are polluting the atmosphere, soil and seas, consuming earth’s energy sources, destroying its forests, extinguishing the habitat of many plants and animals, and poking holes in the ozone layer. Within less than a century, modern life has changed the delicate balance built on earth for millions of years, threatening to destroy it. It is our role to avert this process, and the question is how we do it.

I naively would like to think that the answer is hidden in one single word--leadership. Leadership that places education in all levels--from kindergarten through university and even adult education--at the very top of its priorities. Leadership that invests in education because it deeply believes that education will not only generate the next generation of scientists, physicians, engineers, writers, musicians, philosophers, architects, and artists, but also that it has the wonderful ability to dissipate fundamentalism, to build mutual respect and understanding among people and nations, and to convert religions into a platform of peaceful dialogue among people. Leadership that allows people to be free, enabling them to fly on the wings of their imagination. Leadership that can see beyond the borders of a nation and understands that the world’s problems cannot be solved without international cooperation: a river or atmosphere contaminated in one country will contaminate the water resources people drink from and the air they breathe in its neighboring countries. Leadership that knows that human beings are not the only living organisms on earth and that we must be considerate of our environment. Leadership that has learned the lesson of history that bloodshed never ends and only leads to more bloodshed. The solution to conflicts should be found at the negotiating table, not on the battlefield. That was the dream of the prophet Isaiah (chapter 2, verse 4): “And they shall beat their swords into plowshares, and their spears into pruning hooks: nation should not lift up sword against nation, neither shall they learn war anymore.” Leadership that replaces ideology with a national ethos, that defines targets and gives its people a purpose, making them want to live in their own countries, preserving their history and culture, and at the same time making them prosper. Leadership that understands that dignified human life is a value well above all others.
TO THE EDITORS:

David Hazony paints a bleak picture of Israeli education in his article “Higher Concerns” (Azure 27, Winter 2007). Sadly, it does not do full justice to the grim reality. We in Israel are mired in an education crisis far deeper and wider than Hazony describes. Even if Israeli academia were to be restored to its former glory apropos the study of Judaism and the humanities, it is questionable whether this would be sufficient to cure the malaise affecting Israel’s current leadership, which is, in my opinion, akin to that of a terminally ill patient.

Schooling, education, and culture in general have lost their prestige as essential Israeli values, and have been marginalized in the face of frighteningly cynical economic and political forces. Science and technology are now the driving forces behind Israel’s economic growth, but there can be no effective education in these fields without a corresponding investment of effort and resources in the study of the tradition, history, and archaeology of the Jewish people in Israel and the diaspora. Science and technology are universal subjects, independent of nationality, and one can study them and excel at them anywhere in the world. Israel is certainly not the best place to learn or build a career in these professions. Thus, anyone wanting to learn and apply them in Israel must do so out of a sense of national responsibility and a desire to contribute to the advancement of his country. Therefore, he needs to grow up in an atmosphere in which it is clear to him why he must study and work here and not somewhere else—and the “here” is the Israel Institute of Technology in Haifa (the Technion), the Hebrew University of Jerusalem, Ben-Gurion University of the Negev, Bar-Ilan University, and the Universities of Tel Aviv and Haifa, whose names bear the imprint of the history of the land of Israel and the Jewish nation that built it.

I deeply regret that I cannot see anyone in the ranks of today’s leadership who acts out of a true concern for the promotion of the country’s spiritual affairs, and whose past and present actions serve as an example and a model to be imitated and esteemed. I cannot identify a single leader who could inspire the multitudes to social, educational, and cultural activism. The rifts in Israeli society that have spawned extremist political and religious factions have blighted us with phenomena such as draft evasion, drug addiction, and horrifying levels of verbal and physical violence. They have also marginalized education and culture, and have left our schools to play the meager technical role of training experts in various fields—a role in which they have no guarantee of long-term success in the face of fierce competition in the international arena.

In a relatively short period of sixty years, then, we have succeeded in building something magnificent—namely, a Jewish state—and then destroying it with our own hands. We have turned our backs on everything that contributed to that extraordinary creation, including the culture of learning in all the Jewish diasporas, and have attempted to copy, unsuccessfully, the developed countries of the West in an effort to be just like every other nation. We have hacked
away at the rich and varied Jewish cultures of the world in an attempt to create an “Israeli” culture that lacks substance and meaning. The result is a superficial amalgam that is slowly dissolving into a swamp of corruption and cynicism.

The era of Israel’s founder, David Ben-Gurion – who, in even darker days for our country, started a Jewish Bible study group in his own home, and authored the book *Ben-Gurion Looks at the Bible* – ended all too soon, and certainly before it managed to put down strong roots. Indeed, the idea that one of this country’s leaders would study and teach the Bible in his home seems quite absurd today.

“Everything is possible… if we invest well in knowledge.”

--Dr. Ciechanover

“So how do we bring about a world where the riches of life are shared by all humanity, where they are not limited to the lucky – those relatively few who happen to live in the developed world? Education is the answer. All good things emanate from it. If young people are educated well, they will be citizens of the world, able to understand its challenges, knowing what is needed to address them. Such people will turn their backs on terror and extremism and will direct their talents and knowledge toward changing their own countries and benefiting all of humanity.”

--Aaron Ciechanover, excerpted from “The Paradox,” a chapter in the book *The Way We Will Be 50 Years From Today: 60 of the World’s Greatest Minds Share Their Vision of the Next Half Century*
Studies in Despair

Special: The Two Israeli Nobel Prize Laureates Foresee a Gloomy Future for the State

By Sever Plocker
Yediot Aharanot
October 28, 2006

(Translation from Hebrew)

From a political point of view, they are poles apart, but on one topic Prof. Yisrael Aumann and Prof. Aharon Ciechanover are of the same opinion: Pitiful and failed leadership is leading Israel to destruction. What worries them most is the deterioration in academics and education: "There is a close connection between the sinking of the Israeli spirit and the downfall of the State," they warn. "Everything here seems lacking in values, temporary, one patch on top of another, a thin bandage that can be torn off with any breeze."

Two men, neither young, looked into each other's teary eyes. Behind them, on a green chalkboard, were written complex formulae. They shared stories of their experiences, but not in chemistry or in mathematics. They spoke with enthusiasm and uplifted spirits about Hassidic niggunim [melodies] and Jewish prayers. Their voices cracked, their chins trembled. In a minute, I thought, they will break down crying. It was close.

The two men, Prof. Yisrael (Robert) Aumann and Prof. Aharon Ciechanover, are Israeli scientists and Nobel Prize winners. The weekend supplement to Yediot Aharanot had arranged a discussion between them on the subject of the weakening of the Israeli spirit and the failings of the Israeli leadership. I was there to report on what was a deep, painful, gloomy, and sometimes truly frightening discussion, one that leaves the listener with very little hope and a great deal of discomfort.

The State of Israel, say the two professors, who are poles apart in their political views, is moving in the wrong direction. It is being swept away into the darkness, headed on a path toward possible destruction—and not because of our external enemies. Rather, we have only ourselves to blame: ourselves and our leaders, or those who call themselves our leaders.

Aumann and Ciechanover found a way out of their shared pessimism in their Jewish roots. "As a scientist, I am only a tourist in the palace of the Holy One, blessed be he," said Ciechanover, "who discovers secrets of the universe that he created, systems that were hidden in it for millions of years. If there are apparent flaws in them, I try, through medicine and science, to fix them."

Aumann stroked his white beard...and said, "I feel the same way you do – I feel the same way you do."

Were their eyes full of tears at the end of their discussion because of the emotions aroused by the memory of the Hassidic niggun? That was not my impression. From time to time, in speaking of
the fate of Israel and the failure of its leaders, Ciechanover and Aumann sounded like people on the verge of tears – two outstanding scientists who are tormented by fear for the future of our State.

The discussion began with my question, Are any more Israelis expected to win Nobel Prizes? "The question is totally irrelevant," answered Ciechanover. "The Nobel Prize," he explained, "is a rare event – rarer than the chance of being struck by lightning on a sunny day."

Ciechanover: "The State does not have to aspire to Nobel Prizes as a national agenda. So what if three people who received Nobel Prizes live here? What Israel needs is a broad educational system, a critical mass of researchers and philosophers and ethicists and men of letters who will lead her."

And there is no critical mass like that?

Prof. Ciechanover: "There is academic deterioration at all levels. Even among people with academic degrees, I find garbled language, a lack of cultural depth, and ignorance of general history and of the history of the Jewish people. We need institutions of higher learning headed by path-breaking leadership, but that kind of leadership has disappeared. Where are the outstanding men of letters of the past? I see a close connection between the sinking of the Israeli spirit and the downfall of the State. Without developed humanities and Jewish studies, quality science of any kind cannot exist in the State of Israel – not physics, nor chemistry, nor mathematics, nor medicine. In order to flourish, scientists of nature and technology must be nourished by the humanities: by ethics, philosophy, literature, history, and Judaism.

"The fact that the State of Israel has not become the great world center for Jewish thinking and history," says Prof. Ciechanover, "is our greatest cultural bankruptcy. If we do not have here, in the Hebrew University in Jerusalem, the leading world center for Jewish historical research, it is proof of the fact that we have gone bankrupt."

Prof. Aumann: "You are one hundred percent correct."

How did the academic downfall and spiritual diminution begin?

Prof. Ciechanover: "The downfall began long before the demise of the university: It began in the lower schools. I have no doubt of it. It is, first of all, the ongoing erosion of the status of the teacher, the main reason for which is the frequent changes in the head of the Ministry of Education. Long-term reforms in education take dozens of years; in the Israeli political reality, this is simply impossible. Does the name 'Dovrat Commission' [the most recent national commission on educational reform] still mean something to you? It has already been erased from our memory."
Have we betrayed education?

Prof. Ciechanover: "We have betrayed education and therefore betrayed everything. For the State of Israel, education, academia, the humanities are everything. Unfortunately, not even one of the country's universities is rated among the 100 outstanding universities in the world. The President of the Hebrew University will tell you, and the President of the Technion will tell you, and the soon-to-retire President of Tel-Aviv University will tell you: we are not capable of bringing new scientists to Israel, nor are we capable of seeking them out, as we are constantly forced to cut and cut and cut our budgets."

Prof. Aumann: "Our academic failure is not only a budgetary problem. The professors all cry that we need more money for education and for the universities. Even the doctors demand more money for medicine and road planners more money for infrastructure – as we say in the Neilah prayer on Yom Kippur, 'Many are the needs of Your people, and their understanding is limited.' We don't have to appeal to the State budget and the Ministry of the Treasury for everything. Sometimes one has to do things differently."

How differently?

Prof. Aumann: "Instead of putting one's hand in the public's pocket, one can appeal to private sources. We can raise large contributions for humanities departments, and for the teaching of Judaism as well, and "sell" donors on the importance of these fields for the protection of Israel and its future. But this is still not enough. I also support an extreme increase in tuition at the universities; I would increase it ten times…At the same time, I would increase [government] stipends and grant generous loans on special terms. There is no need for the State of Israel to subsidize every student in the field of business administration or finance or technology. Let them pay a realistic tuition, or take loans, and when they receive high salaries, which are standard in these professions, they will gradually pay back the debt. But there is a definite need to subsidize the humanities, where the jobs do not offer large salaries. The state should grant them stipends and forgive the loans. If you go to law school and pay NIS 140,000 per year and later become a successful lawyer in the business world, then you certainly have to return the money that you received from the state. This is just, this is right. This is also how it works in America, where the leading universities are not public, but rather are organized as non-profit associations."

But in Israel there is no tradition of business corporations that contribute, shall we say, NIS 50,000,000 to the Faculty of the Humanities or the department of Jewish history at one of the universities.

Prof. Ciechanover: "Even if such a corporation could be found, I don't see this as the desired solution. Three national matters in Israel – education, health, and security – must be the responsibility of the State. These are the foundation stones of our existence here; the State of Israel cannot entrust education to private hands. Who will fund the kindergartens and the high
schools that are not, as is well-known, attractive targets for contributions? Our universities will not exist without a broad educational and academic infrastructure that only the state is capable of maintaining."

**Should we leave the universities outside the arena of the economic game?**

Prof. Ciechanover: "Not entirely. I do support the system of stipends and loans and rewarding members of the faculty according to their achievements, as none other than the Ministry of the Treasury proposed. I cannot accept a situation in which a faculty member who brings in research grants, draws attention [to his university], trains students, works publicly in the university, and is concerned about his community can receive in shekels, down to the last agora, the same salary as a member of the faculty who sits idly with his legs crossed and does nothing. Economic competition in certain fields in the universities is critical for moving the wheels of the system."

**You could have "starred" in any university in the world. Why are you here?**

Prof. Ciechanover: "Because I was born here and I want to live in a Hebrew-speaking environment, in the State that I fought for and in which I believe—on account of the long history of my people—it is important to live. This country is the essence of my existence. My parents came to Israel as Jews from Poland because they wanted to establish a state in which no one would call them Zhid—a Jewish state in which they could live a free life. They knew what they were aiming for. But this is not necessarily true of all Israelis. Our internal cohesion is falling apart; the rifts are growing from within.

"I grew up with clear values, and, to my sorrow, I see around me their steady erosion. At this juncture, we have lost sight of our goal, and have no one with his hand on the rudder."

Prof. Yisrael Aumann is a Haredi Jew; Prof. Aharon Ciechanover describes himself as a religious Jew: "The only music that I listen to," he tells me, "is cantorial selections. I have a huge collection of them. I grew up in a home with a deep-rooted Jewish culture. I truly and honestly believe that we will not achieve success in physics if we do not also study Jewish philosophy and Jewish ethics and the history of the Jewish people. These things are interdependent."

**Are we at the edge of the abyss? Is Israel in danger?**

Prof. Ciechanover: "Yes, and if we do not regain our balance, we will cease to exist. I say this in very clear language: If we don't change, we will cease to exist. We will be uprooted from this place."

Prof. Aumann: "I, too, am very pessimistic and depressed. We lack the will to exist, we lack the patience to exist. We lack Zionism with a capital "Z." We have turned into post-Zionists, to our own worst enemies. From my point of view, the blackest moment in the history of the State of Israel, and perhaps in the history of the Jews in the world, was the Tenth of Av 5765."
The day that the evacuation from Gaza started…

Prof. Aumann: "The day that the expulsion started was the blackest moment. This was an unjustified act, immoral, not strategic, not political. It wasn't anything. My people went mad – simply went mad."

Why the people? Why not the leadership?

Prof. Aumann: "Because the leadership is the product of the people; look at the last election results."

Prof. Ciechanover: "Until a few months ago, I would not have agreed with Prof. Aumann. Today, even though I haven't changed my place on the political map, I have no choice but to agree with him. Last year, I was in favor of the idea of disengagement, which seemed to me to be an act of unilateral generosity towards the Palestinians. I hoped that they would respond to us in kind, but I was wrong: after the unilateral disengagement, we received only terror and more terror. The unilateral idea was bankrupt and at the same time the soap bubble [Kadima] that arose from its base went bankrupt. It is indeed still in power, but what is its message today? This party, and with it this entire government, doesn't have even a morsel of an agenda."

What do you actually expect from the government?

Prof. Ciechanover: "I expect the Prime Minister and the Minister of Defense and all the ministers to wake up in the morning and ask themselves: After six months in office, what have we done to this country? Have we achieved even one objective that we set for ourselves and those who elected us? This is the moral minimum demanded of them. I wonder: how can they live with the failure that they created with their own hands?"

You mean, why are they not ashamed?

Prof. Ciechanover: "They are not ashamed because they don't care. They don't think about us. I look at them and I do not know what my future is in this country. I am very, very pessimistic and depressed."

Prof. Aumann: "I am also pessimistic and depressed. But I have not forgotten that this is all our own fault – all our own fault."

In this way the discussion between the two Prize winners, our most distinguished scientists, ended but was not concluded. They parted with a hug, and I saw tears mounting in the corners of their eyes.
“Dialog between the Church and science is important, especially with respect to moral and ethical questions for which science does not have an adequate answer. Even if there is not always agreement between the parties, the fact that there is dialog is important. The Church, which has great influence, can use its power to eliminate prejudices and can also use science and its achievements as a bridge to peace and understanding.”

--Dr. Ciechanover, upon being conferred membership into the Pontifical Academy of Sciences by Pope Benedict XVI in October 2008
Evolution and Religion Can Coexist, Scientists Say

By Stefan Lovgren
National Geographic News
October 18, 2004

"Science without religion is lame; religion without science is blind." —Albert Einstein

Joel Primack has a long and distinguished career as an astrophysicist. A University of California, Santa Cruz, professor, he co-developed the cold dark matter theory that seeks to explain the formation and structure of the universe.

He also believes in God.

That may strike some people as peculiar. After all, in some corners popular belief renders science and religion incompatible.

Yet scientists may be just as likely to believe in God as other people, according to surveys. Some of history's greatest scientific minds, including Albert Einstein, were convinced there is intelligent life behind the universe. Today many scientists say there is no conflict between their faith and their work.

"In the last few years astronomy has come together so that we're now able to tell a coherent story" of how the universe began, Primack said. "This story does not contradict God, but instead enlarges [the idea of] God."

Evolution

The notion that science and religion are irreconcilable centers in large part on the issue of evolution. Charles Darwin, in his 1859 book The Origin of Species, explained that the myriad species inhabiting Earth were a result of repeated evolutionary branching from common ancestors.

One would be hard pressed to find a legitimate scientist today who does not believe in evolution. As laid out in a cover story in the November issue of National Geographic magazine, the scientific evidence for evolution is overwhelming.

Yet in a 2001 Gallup poll 45 percent of U.S. adults said they believe evolution has played no role in shaping humans. According to the creationist view, God produced humans fully formed, with no previous related species.

But what if evolution is God's tool? Darwin never said anything about God. Many scientists—and theologians—maintain that it would be perfectly logical to think that a divine being used evolution as a method to create the world.
Still, science does contradict a literal interpretation of the first chapter of Genesis in the Bible—on the origin of the universe—which says that God created heaven and the Earth and the species on it in six days.

Scientific evidence shows that the universe was actually formed about 13.7 billion years ago, while the Earth was formed around 4.5 billion years ago. The first humans date back only a hundred thousand years or so.

Like other scientists of faith, Primack, who is Jewish and reads the Bible regularly, argues that the Bible must not be taken literally, but should be read allegorically.

"One simply cannot read the Bible as a scientific text, because it's often contradictory," Primack said. "For example, in the Bible, Noah takes two animals and puts them on the Ark. But in a later section, he takes seven pairs of animals. If this is the literal word of God, was God confused when He wrote it?"

Proving God

Science is young. The term "scientist" may not even have been coined until 1833. Ironically, modern physics initially sought to explain the clockwork of God's creation. Geology grew partly out of a search for evidence of Noah's Flood.

Today few scientists seem to think much about religion in their research. Many are reluctant to stray outside their area of expertise and may not feel a need to invoke God in their work.

"Most scientists like to operate in the context of economy," said Brian Greene, a world-renowned physicist and author of *The Fabric of the Cosmos: Space, Time, and the Texture of Reality*. "If you don't need an explanatory principle, don't invoke it."

There is, of course, no way to prove religious faith scientifically. And it's hard to envision a test that could tell the difference between a universe created by God and one that appeared without God.

"There's no way that scientists can ever rule out religion, or even have anything significant to say about the abstract idea of a divine creator," Greene said.

Instead, Greene said, science and religion can operate in different realms. "Science is very good at answering the 'how' questions. How did the universe evolve to the form that we see?" he said. "But it is woefully inadequate in addressing the 'why' questions. Why is there a universe at all? These are the meaning questions, which many people think religion is particularly good at dealing with."

But is a clean separation between science and religion possible? Some scientific work, including such hot topics as stem cell research, has moral and religious implications.

The Echo Foundation 64 The Aaron Ciechanover Project
"Religion is about ethics, or what you should do, while science is about what's true," Primack said. "Those are different things, but of course what you should do is greatly determined by what's true."

**Natural Laws**

In a 1997 survey in the science journal *Nature*, 40 percent of U.S. scientists said they believe in God—not just a creator, but a God to whom one can pray in expectation of an answer. That is the same percentage of scientists who were believers when the survey was taken 80 years earlier.

But the number may have been higher if the question had simply asked about God's existence. While many scientists seem to have no problem with deism—the belief that God set the universe in motion and then walked away—others are more troubled with the concept of an intervening God.

"Every piece of data that we have indicates that the universe operates according to unchanging, immutable laws that don't allow for the whimsy or divine choice to all of a sudden change things in a manner that those laws wouldn't have allowed to happen on their own," Greene said.

Yet recent breakthroughs in chaos theory and quantum mechanics, for example, also suggest that the workings of the universe cannot be predicted with absolute precision.

To many scientists, their discoveries may not be that different from religious revelations. Science advancements may even draw scientists closer to religion.

"Even as science progresses in its reductionist fashion, moving towards deeper, simpler, and more elegant understandings of particles and forces, there will still remain a 'why' at the end as to why the ultimate rules are the way they are," said Ted Sargent, a nanotechnology expert at the University of Toronto.

"This is where many people will find God, and the fact of having a final unanswerable 'why' will not go away, even if the 'why' gets more and more fundamental as we progress," he said.

Brian Greene believes we are taking giant strides toward understanding the deepest laws of the universe. That, he says, has strengthened his belief in the underlying harmony and order of the cosmos.

"The universe is incredibly wondrous, incredibly beautiful, and it fills me with a sense that there is some underlying explanation that we have yet to fully understand," he said. "If someone wants to place the word God on those collections of words, it's OK with me."
Jewish Responses to Modern Science
Coexistence and Conflict

By Rabbi Louis Jacobs
Excerpted from The Jewish Religion: A Companion

The struggle between science and religion in the nineteenth century, although largely engaged in by Christians, was naturally of equal concern to religious Jews. With regard to the basic problem of the scientific approach to the discovery of truth versus religious faith, Jewish thinkers, believing that all truth comes from the One God, generally refused to adopt the "two-truth" theory, according to which religion is in conflict with science but each is "true" in its own sphere.

Relying on the medieval discussions of faith versus reason, the majority of Jewish thinkers who grappled with the problem held that religion has to do with life's values and with a reaching-out to the transcendent, and is therefore fully compatible with scientific views about the composition and workings of the world perceived by the senses.

Knowledge vs. Belief

While Judaism views with favor investigation into the nature of the physical universe--from the religious point of view this increases human perception of the glory of God as manifest in His creation--such investigations are irrelevant to the question of religious faith.

As C. S. Lewis puts it, the scientist, in his field, knows, whereas the religious person believes. In other words, science explains the way in which the universe works as it does, while religion seeks to explain the purpose of the universe and man's place within it. The one is a matter of knowledge, the other a matter of belief.

Very few Jewish thinkers, for instance, felt themselves compelled by their religious faith to hold fast, despite all the new evidence, to the geocentric view of the universe. Far from the new picture of the immense size of the universe (with our whole solar system a mere speck in the vastness of space) destroying faith, they believed that scientific discoveries help to increase man's sense of wonder at the divine wisdom.

The problem for religious Jews is not, therefore, science per se, but the apparent conflict between particular scientific theories and the biblical record: for instance, between the Genesis narrative of spontaneous creation in six days and the theory of evolution, or between the great age of the universe revealed by science and the biblical chronology according to which the world is no more than 5,500 years old.

Reconciling Contradictions

Some Orthodox thinkers here fall back on the idea that scientific theories are only "guesswork," which it is folly to accept in the face of contradiction by the divinely revealed Torah.
But others, like Rabbi Kook, have maintained that the creation narrative has always been held by the tradition to belong to the "mysteries of the Torah," and is therefore open to interpretation. The creation narrative was not intended to be a literal description of how everything came into being, but rather to stress that it was God who called it all into being--and there is no reason why it should not be postulated that He used an evolutionary process to achieve His purpose.

Where science does come into conflict with the tradition is when scientific method is employed to examine the documents of the Jewish religion and to discover how religion itself came to be. Biblical criticism, and sociological and psychological theories about the nature of society and the human personality, do present a challenge to the doctrine of divine revelation.

Some Jewish thinkers have argued that biblical criticism is only conjectural, and sociology and psychology are not exact sciences. Orthodox thinkers still pursue this line, at least so far as criticism applied to the Pentateuch, the very word of God, is concerned. Reform and Conservative thinkers hold that, indeed, the application of scientific method in these areas has to be accepted even if the conclusions reached demand a new approach to the whole question of revelation.

**Following Doctor's Orders**

In connection with the science of medicine, all Orthodox thinkers welcome wholeheartedly the tremendous advances in this sphere. Already in the period of the *geonim* the view was held that the talmudic rabbis only had the medical knowledge of their day, so one must not rely on remedies found in the Talmud, for all the authority the Talmud possesses is in matters of religion and law. In matters of Jewish law such as whether a person who is sick should eat on Yom Kippur, it is for the doctor—not the rabbi—to decide, and the doctor's knowledge is based on the advance of modern medicine.

Scientific advances have, indeed, posed new problems for Jewish law and ethics--organ transplants and artificial insemination are obvious examples--but no Jewish thinker has expressed the view that, because of the problems to which it gives rise, the advance of science should be halted.
Profile: Professor Aaron Ciechanover

For the September 2009 issue (No. 4) of Rambam On Call, a publication of Rambam Health Care Campus, Israel’s largest medical center, writer and editor Dvora Kreda interviewed Dr. Ciechanover in his office at the Technion. What follows is an excerpt from that interview.

On the bookshelves behind glass are numerous textbooks: cell biology, biochemistry, physiology, internal medicine, hematology, endocrinology, surgery, pediatrics. Many address methods in biochemistry and molecular biology.

"This is my professional library, the books that I use daily," the Professor comments, "science and medicine, and obviously the Jerusalem Bible, which I take with me everywhere and have [a copy of] wherever I have a library. I love it because it is artistically made and, literally, it's written in a way that transmits the spirit of the Bible and the centrality of Jerusalem in Jewish life."

Does Prof. Ciechanover, then, for all his focus on a visible and tactile reality, believe in God's existence?

He answers, or perhaps evades, the question with a series of rhetorical questions of his own. "Whichever answer I shall give you will put me in trouble. My Jewish religious friends will hate my scientific answer, and my colleagues in science will hate my Jewish religious answer. Which God? A Jewish God, a God associated with any particular religion, or any God -- a kind of power beyond our understanding that stands behind the creation of the universe and life and the wonderful order and laws of nature? We are human beings living in a complex and wonderfully diverse world made of numerous peoples, cultures and histories, religions and beliefs, languages and arts -- a celebration of diversity; each of us derives his or her values from multiple sources and the rich environment in which we have grown, and what we are and believe is a synthesis of these multiple springs that irrigate us.

"You see here religious artifacts: a mezuzah; from the Jewish museum in Athens, a replica of a Hannukiah that was lighted by the Jews of Salonica – it was a huge Jewish community, but most of them were murdered [in the Holocaust]; a collection of Central European cantorial music records -- I listen to Jewish liturgical music, whose prayers and songs are a deep part of my culture, more than to any other music."

On the wall are a photo of Prof. Ciechanover with Pope Benedictus the XVI, and two naïve paintings of Noah's Ark by Spanish South-American Christian artists. "The network of the Jewish religion as well as, I believe, that of many other religions, is intricate," he comments, "and non-Jewish beliefs have strong spiritual, historical and artistic connections to our religion.

"And here is a Buddhist daruma," he says, lifting from its place on his desk beside the computer monitor a beautiful roly-poly doll of dark wood, caressing it in his palm, and turning it to display the Japanese characters in which the sculptor has carved his signature. "Lay it down, it comes [back] up," he demonstrates. "The idea is that whenever you fall, you can and must rise up again.
You look at him, and you think how much symbolic wisdom is embedded in this hand-carved wooden doll."

He is asked about a Talmud class in which he and several other physicians and scientists participate. "It's about the relationship between Halacha [Jewish law] and modern medicine," he answers. "There is no problem in modern medicine without a precedent to learn from in the old Jewish scriptures," he adds. "If you take yeshiva scholars who are ready to take upon themselves general education, you find people with excellent minds and sharpened brains, which tells me that Jewish scholarliness is similar to scientific investigative methods. Both use logic: if you are developing a Talmudic argument, it's like LEGO, everything has to fit logically. Analyzing a biological process follows the same basic rules, but here logic is represented by laws of nature that cannot be violated."

He is asked whether he thinks it is a coincidence that of the ten Nobel Laureates that gathered at the Technion in May 2008 for a Landmarks in Science Symposium, so many, according to their bio-sketches, hail from very modest backgrounds – the son of a baker, for example, or the son who helped his parents in their restaurant after school and on weekends -- or had fled war, escaped political or social chaos, or endured other kinds of adversity during childhood.

"My parents came from Poland," Prof. Ciechanover answers. "My father was a legal clerk and later a lawyer, and my mother was an English teacher. They were persecuted by anti-Semites there, and built a small family here and bequeathed to us an education in [moral] values, and that has to do with tolerance, with humbly recognizing the complexity of the world around us, the diversity of people, cultures and religions and the sanctity of human life and health.

"I don't know about class as a [common] denominator for Nobel Prize winners," he continues, [but by] now I know many [Laureates] and, first, they are human beings with all that implies. Secondly, most of them are humble by nature, humble and curious, because they understand the complexity of nature and the basic fact that the more we know, the more we are aware of how much we know not. For every question that we answer, ten more questions open. [Laureates] are aware that knowledge generates more ignorance or, as nicely defined by [2004 Nobel Laureate in Physics] David Gross, who speaks of the endlessness of knowledge, “we generate intelligent ignorance.”"
The Vega Science Trust: An Interview
with Dr. Ciechanover

The following text is an excerpt from a video interview with Dr. Ciechanover that was conducted by the Vega Science Trust in 2006. It was transcribed by Kitengie Milka Shisso of The Echo Foundation.

Vega: Do you believe in the supernatural? Do you believe there is a God?

Dr. Ciechanover: No. Obviously not. We shouldn’t go that far. For me Judaism is a culture, a culture imbedded deep in the history of these people, with the rights to their own land, with the Holocaust, the persecution, the long years, inquisition…So for me it’s basically a culture that is embedded in history, in archeology and the site that this particular space on which we have absolute rights. And that’s it. I don’t believe in any particular God that sits and directs me or anything; though the prayer book for me is a rich poetry. I happen to be Jewish. I could imagine myself being born to a Confucian family or Buddhist family or Catholic or Protestant or Unitarian and I happened to be born in Israel and to absorb values from my parents and we cannot, we don’t want to even relieve ourselves from these bondages. I feel obliged to those. But I understand that it’s random, I mean, that’s it. But I take it more seriously in the sense…that I think that one of the greater treasures that we have as human beings is our diversity on the planet. And we should be very careful not to flatten the world vis-à-vis Thomas Friedman’s new bestseller The World is Flat and advance scientifically and technologically but at the same time preserve our self identity as people, as individuals, our self identity as nations, our culture, our archeology, history, everything that makes the world such a fascinating one rather than an email and interneting platform, which is so flat. It’s a device.

Vega: I just want to ask, you don’t then believe in any kind of afterlife or any consciousness, a God-like consciousness…

Dr. Ciechanover: No… I don’t believe in anything that is beyond life. I believe in being born, and then there is one factual, once we are born we are going to die. That’s the only fact that I believe in. Nevertheless I am a strong Jew, maybe a religious Jew will not accept it, what I am saying now. But it’s ok. I mean, I am not preaching for acceptance of my own beliefs. Maybe they feel differently about God and about the services and prayer and obedience in their lives. For me, no, it’s a culture, but I feel extremely strong about what all this culture means.
Waging Peace: Middle Eastern Scientists Promote Peace at Malta Conference

By Robyn Velasquez
Washington Report on Middle East Affairs
January/February 2006

PEACE in the Middle East took a giant step forward from Nov. 5 to 10, when some 67 chemical scientists from Israel, Egypt, Iran, Saudi Arabia, Jordan, Lebanon, Kuwait, the Palestinian territories, United Arab Emirates, Bahrain, Qatar and Turkey met on the island of Malta. While the dialogue was between high-level scientists (including six Nobel Laureates) rather than government officials, peace was definitely on the agenda.

The brainchild of Zafra M. Lerman, an Israeli-born chemistry professor and head of the Institute for Science Education and Science Communication at Columbia College Chicago, the meeting is the second major gathering for most members of this elite group. The first was held in Malta in December 2003, and both were organized by the Subcommittee on Scientific Freedom and Human Rights of the International Activities Committee of the American Chemical Society.

Lerman believes that scientists, instead of politicians and diplomats, can lead the way to peace and cooperation in the Middle East. “Scientists care more about scientific freedom and discovery than territorial issues,” she observed. “They need the access to information and shared resources that come from collaboration, not warfare or hostility.”

From the meeting’s opening day, Lerman said, this year’s Malta conference (affectionately known as Malta II) was like a “family reunion with no hostilities or animosities—only friendship.” And since returning from Malta, Lerman, a former member of the Israeli army, has found her e-mail box overflowing with messages of congratulations and friendship from participants and other well-wishers.

Keynote addresses were presented by Nobel Laureates Aaron Ciechanover, Israel Institute of Technology, Israel; Richard R. Ernst, Swiss Federal Institute of Technology in Zurich, Switzerland; Roald Hoffmann, Cornell University, USA; Yuan T. Lee, Academia Sinica, Taiwan; Jean-Marie Lehn, Université Louis Pasteur, France; and F. Sherwood Rowland, University of California, USA.

The program included workshops on science education; water and environment; bio- and chemical sensing; medicinal and natural products; nanotechnology; and solar energy.

A number of new initiatives were developed at the conference. Participants in the education workshop plan to develop Middle East standards for science education, while nanotechnology workshop participants will conduct three workshops in three different countries before the next conference.
The scientists also continued to make progress on last year’s initiatives, including a joint water purification project by Israeli and Palestinian participants. Dr. Y.T. Lee will continue to offer fellowships for Middle East scientists to train with him at the synchrotron in Taiwan; the Israel Institute of Technology will grant three more full scholarships to students from Arab countries; Hoffmann will organize more workshops in the Middle East for graduate students and young faculty members; and for the first time the Weizmann Institute of Science in Israel will begin accepting Palestinian students into its advanced degree programs.

While the group unanimously approved a proposal to hold Malta III in approximately two years, many of the participants made plans to meet before then to continue the scientific exchange.
Social Interest

Chapter Study Questions

1. Compare and contrast the Israeli and United States educational systems.

2. Why is education important? What is the significance of education (to the world/humanity/social justice/development)?

3. What are the U.S. educational system flaws and benefits? How do they compare to the Israeli system? After a thorough investigation of the two systems, would you rather study here or in Israel? Why?

4. Do you think that American students are more aggressive towards their education than students in other countries? Why or why not?

5. Do you agree with President Kajiyama’s belief that students should be independent from their professors?

6. What are some suggestions you may have for educational authorities that will increase students’ enthusiasm for learning?

7. Would you agree with President Kajiyama that children in America “know the joy of asking questions and have their own ideas?” Why or why not?

8. Dr. Ciechanover’s asserts that “teaching in elementary school and kindergartens has become a second grade profession.” Do you believe that this is true in the United States? If so, what can be done to reverse this poor regard for the teaching profession?

9. Reflecting on previous questions and the article beginning on page 52, what are some steps you can take as a student, or perhaps as a future scientist, that will help you to avoid being complacent in the lack of independent thinking? And how can you make the most of every opportunity that crosses your path?

10. Think about Dr. Ciechanover and Dr. Aumann’s concerns for the future of Israel. Put yourself in their shoes, as a major scientist in the U.S. entrusted with great responsibilities. If America was in the same position, what would you do in terms of taking initiative for the reconstruction of the state’s educational system?

11. Explain why Dr. Ciechanover didn’t want to “star” in any other university except in Israel?

12. What do you think of Dr. Ciechanover and Prof. Aumann’s shared opinion that Israel is in a state of “academic downfall” and “spiritual diminution?” What makes the two so pessimistic about the future of Israel as it stands? Do you agree? Explain.

13. Do you think that Israel has a chance to become a united nation once more, with strong leadership in the government and a stable educational system with a strong Jewish culture? Why or why not?

14. Why do you think Dr. Ciechanover believes it is so important for Jewish culture to remain tied to Israeli education (see editorial written by Dr. Ciechanover, page 57)?
15. Do you think it is important to maintain this tie between culture and education? Why or why not? What are some examples of culture being incorporated into the U.S. education system?

16. Explain why Dr. Ciechanover states in his article “The Lessons of Leadership” that the achievements of science and technology described as double-edged swords.

17. Dr. Ciechanover believes that education is the key to building “mutual respect and understanding among people and nations” and converting “religions into a platform of peaceful dialogue.” Do you agree or disagree? Why?

18. There are currently many nations where education is repressed or deficient, resulting in more and more generations of intolerance and inhumanity. In which countries would you consider this to be the case? What factors do you think have led to this result? In what ways can the global community change this problem?

19. Do you think there is a conflict between science and religion? Do you think that it is necessary for there to be dialogue between science and religion? Why or why not? How do you reconcile your own beliefs?

20. Imagine you are having a conversation with Albert Einstein and he tells you that “Science without religion is lame; religion without science is blind.” What does this statement mean to you? How would you respond?

21. Do you think that the disputes between science and religion in the article from the National Geographic News are still relevant today?

22. Would you agree with physicist Brian Greene that science and religion can coexist? Should they coexist? Why or why not? If so, how can the dispute be resolved so that science and religion can coexist?

23. What do you make of Dr. Ciechanover’s rejection of so many traditional Jewish religious beliefs? How does the Jewish identity transcend religion?

24. Do you agree with the statement in the “Waging Peace” article on page 73 that “scientists, instead of politicians and diplomats, can lead the way to peace and cooperation in the Middle East”? Why or why not? In what ways might this be possible?

25. What do you know about the conflict between the Israelis and Palestinians? Discuss the reasons why you think this conflict has been ongoing for over 60 years. Do you think this conflict can be resolved? If so, how?
IV. Discovery of Ubiquitin-Mediated Protein Degradation

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“…the Ubiquitin system is tremendously important. We discovered that the body actually invests more energy in destroying proteins than in producing them. The Ubiquitin system is involved in countless biological processes from the very beginning to the very end of our lives…”

--Dr. Ciechanover, in an interview with VIB News
Alfred Nobel – His Life and Work

By Nils Ringertz
www.nobelprize.org

Alfred Nobel was born in Stockholm on October 21, 1833. His father Immanuel Nobel was an engineer and inventor who built bridges and buildings in Stockholm. In connection with his construction work Immanuel Nobel also experimented with different techniques for blasting rocks.

Alfred's mother, born Andriette Ahlsell, came from a wealthy family. Due to misfortunes in his construction work caused by the loss of some barges of building material, Immanuel Nobel was forced into bankruptcy the same year Alfred Nobel was born. In 1837 Immanuel Nobel left Stockholm and his family to start a new career in Finland and in Russia. To support the family, Andriette Nobel started a grocery store, which provided a modest income. Meanwhile Immanuel Nobel was successful in his new enterprise in St. Petersburg, Russia. He started a mechanical workshop which provided equipment for the Russian army and he also convinced the Tsar and his generals that naval mines could be used to block enemy naval ships from threatening the city.

The naval mines designed by Immanuel Nobel were simple devices consisting of submerged wooden casks filled with gunpowder. Anchored below the surface of the Gulf of Finland, they effectively deterred the British Royal Navy from moving into firing range of St. Petersburg during the Crimean war (1853-1856). Immanuel Nobel was also a pioneer in arms manufacture and in designing steam engines.

Successful in his industrial and business ventures, Immanuel Nobel was able, in 1842, to bring his family to St. Petersburg. There, his sons were given a first class education by private teachers. The training included natural sciences, languages and literature. By the age of 17 Alfred Nobel was fluent in Swedish, Russian, French, English and German. His primary interests were in English literature and poetry as well as in chemistry and physics. Alfred's father, who wanted his sons to join his enterprise as engineers, disliked Alfred's interest in poetry and found his son rather introverted. In order to widen Alfred's horizons his father sent him abroad for further training in chemical engineering. During a two year period Alfred Nobel visited Sweden, Germany, France and the United States. In Paris, the city he came to like best, he worked in the private laboratory of Professor T. J. Pelouze, a famous chemist. There he met the young Italian chemist Ascanio Sobrero who, three years earlier, had invented nitroglycerine, a highly explosive liquid. Nitroglycerine was produced by mixing glycerine with sulfuric and nitric acid. It was considered too dangerous to be of any practical use. Although its explosive power greatly exceeded that of gunpowder, the liquid would explode in a very unpredictable manner if subjected to heat and pressure. Alfred Nobel became very interested in nitroglycerine and how it
could be put to practical use in construction work. He also realized that the safety problems had to be solved and a method had to be developed for the controlled detonation of nitroglycerine. In the United States he visited John Ericsson, the Swedish-American engineer who had developed the screw propeller for ships. In 1852 Alfred Nobel was asked to come back and work in the family enterprise which was booming because of its deliveries to the Russian army. Together with his father he performed experiments to develop nitroglycerine as a commercially and technically useful explosive. As the war ended and conditions changed, Immanuel Nobel was again forced into bankruptcy. Immanuel and two of his sons, Alfred and Emil, left St. Petersburg together and returned to Stockholm. His other two sons, Robert and Ludvig, remained in St. Petersburg. With some difficulties they managed to salvage the family enterprise and then went on to develop the oil industry in the southern part of the Russian empire. They were very successful and became some of the wealthiest persons of their time.

After his return to Sweden in 1863, Alfred Nobel concentrated on developing nitroglycerine as an explosive. Several explosions, including one (1864) in which his brother Emil and several other persons were killed, convinced the authorities that nitroglycerine production was exceedingly dangerous. They forbade further experimentation with nitroglycerine within the Stockholm city limits and Alfred Nobel had to move his experimentation to a barge anchored on Lake Mälaren. Alfred was not discouraged and in 1864 he was able to start mass production of nitroglycerine. To make the handling of nitroglycerine safer Alfred Nobel experimented with different additives. He soon found that mixing nitroglycerine with silica would turn the liquid into a paste which could be shaped into rods of a size and form suitable for insertion into drilling holes. In 1867 he patented this material under the name of dynamite. To be able to detonate the dynamite rods he also invented a detonator (blasting cap) which could be ignited by lighting a fuse. These inventions were made at the same time as the diamond drilling crown and the pneumatic drill came into general use. Together these inventions drastically reduced the cost of blasting rock, drilling tunnels, building canals and many other forms of construction work.

The market for dynamite and detonating caps grew very rapidly and Alfred Nobel also proved himself to be a very skillful entrepreneur and businessman. By 1865 his factory in Krümmel near Hamburg, Germany, was exporting nitroglycerine explosives to other countries in Europe, America and Australia. Over the years he founded factories and laboratories in some 90 different places in more than 20 countries. Although he lived in Paris much of his life he was constantly traveling. Victor Hugo at one time described him as "Europe's richest vagabond". When he was not traveling or engaging in business activities Nobel himself worked intensively in his various laboratories, first in Stockholm and later in Hamburg (Germany), Ardeer (Scotland), Paris and Sevran (France), Karlskoga (Sweden) and San Remo (Italy). He focused on the development of explosives technology as well as other chemical inventions, including such materials as synthetic rubber and leather, artificial silk, etc. By the time of his death in 1896 he had 355 patents.

Alfred Nobel's laboratory in Bofors, Sweden
Intensive work and travel did not leave much time for a private life. At the age of 43 he was feeling like an old man. At this time he advertised in a newspaper "Wealthy, highly-educated elderly gentleman seeks lady of mature age, versed in languages, as secretary and supervisor of household." The most qualified applicant turned out to be an Austrian woman, Countess Bertha Kinsky. After working a very short time for Nobel she decided to return to Austria to marry Count Arthur von Suttner. In spite of this Alfred Nobel and Bertha von Suttner remained friends and kept writing letters to each other for decades. Over the years Bertha von Suttner became increasingly critical of the arms race. She wrote a famous book, *Lay Down Your Arms* and became a prominent figure in the peace movement. No doubt this influenced Alfred Nobel when he wrote his final will which was to include a Prize for persons or organizations who promoted peace. Several years after the death of Alfred Nobel, the Norwegian Storting (Parliament) decided to award the 1905 Nobel Peace Prize to Bertha von Suttner.

Alfred Nobel's greatness lay in his ability to combine the penetrating mind of the scientist and inventor with the forward-looking dynamism of the industrialist. Nobel was very interested in social and peace-related issues and held what were considered radical views in his era. He had a great interest in literature and wrote his own poetry and dramatic works. The Nobel Prizes became an extension and a fulfillment of his lifetime interests.

Many of the companies founded by Nobel have developed into industrial enterprises that still play a prominent role in the world economy, for example Imperial Chemical Industries (ICI), Great Britain; Société Centrale de Dynamite, France; and Dyno Industries in Norway. Toward the end of his life, he acquired the company AB Bofors in Karlskoga, where Björkborn Manor became his Swedish home. Alfred Nobel died in San Remo, Italy, on December 10, 1896. When his will was opened it came as a surprise that his fortune was to be used for Prizes in Physics, Chemistry, Physiology or Medicine, Literature and Peace. The executors of his will were two young engineers, Ragnar Sohlman and Rudolf Lilljequist. They set about forming the Nobel Foundation as an organization to take care of the financial assets left by Nobel for this purpose and to coordinate the work of the Prize-Awarding Institutions. This was not without its difficulties since the will was contested by relatives and questioned by authorities in various countries.
About the Nobel Prizes

www.nobelprize.org

On 27 November 1895, a year before his death, Alfred Nobel signed the famous will which would implement some of the goals to which he had devoted so much of his life. Nobel stipulated in his will that most of his estate, more than SEK 31 million (today approximately SEK 1,630 million)\(^1\) should be converted into a fund and invested in "safe securities."

The income from the investments was to be "distributed annually in the form of prizes to those who during the preceding year have conferred the greatest benefit on mankind."

The Nobel Prize amount for 2009 is set at Swedish kronor (SEK) 10 million per full Nobel Prize.

Award Ceremony

The Nobel Laureates take center stage in Stockholm on 10 December when they receive the Nobel Prize Medal, Nobel Prize Diploma and document confirming the Nobel Prize amount from King Carl XVI Gustaf of Sweden. In Oslo, the Nobel Peace Prize Laureates receive their Nobel Peace Prize from the Chairman of the Norwegian Nobel Committee in the presence of King Harald V of Norway. An important part is the presentation of the Nobel Lectures by the Nobel Laureates. In Stockholm, the lectures are presented days before the Nobel Prize Award Ceremony. In Oslo, the Nobel Laureates deliver their lectures during the Nobel Peace Prize Award Ceremony.

Nominations for 2010

237 names were submitted for the 2010 Nobel Peace Prize, 38 of which are organizations. The Nobel Committees in Physics, Chemistry, Physiology or Medicine, Literature and the Prize Committee for Economic Sciences each usually receives 250-300 names every year, but this is the highest number of nominations for the Nobel Peace Prize ever. The names of the nominees cannot be revealed until 50 years later.

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\(^1\) As of June 30, 2010, the official United States Government exchange rate is 1 USD = 7.734 SEK. Therefore, 1 SEK = 0.1293 USD. Source: Financial Management Service of the United States Department of Treasury.
The Nobel Prize medals for Physics and Chemistry, Physiology or Medicine, and Literature were modeled by Swedish sculptor and engraver Erik Lindberg, while the Peace medal was created by Norwegian sculptor Gustav Vigeland. The medal for the Economics Prize, which was not established until 1968, was designed by Swede Gunvor Svensson-Lundqvist.

The front side of the three “Swedish” medals (Physics and Chemistry, Physiology or Medicine, and Literature) is the same, featuring a portrait of Alfred Nobel and the years of his birth and death in Latin, while the images on the back vary according to the symbols of the respective prize-awarding institutions. The main inscription on the reverse side of these three medals is the same: "Inventas vitam juvat excoluisse per artes," which means “Inventions enhance life which is beautified through art.” The Peace medal has the inscription "Pro pace et fraternitate gentium," which means "For the peace and brotherhood of men," and the Economics medal has no quotation on the reverse. On all "Swedish" Nobel medals the name of the Laureate is engraved fully visible on a plate on the reverse, whereas the name of the Peace Laureate as well as that of the Winner for the Economics Prize is engraved on the edge of the medal, which is less obvious.

Up until 1980 the medals, each weighing approximately seven ounces and with a diameter of just over two and a half inches, were made of 23-karat gold. Since then they have been made of 18-karat green gold plated with 24-karat gold. The Peace medal is cast by the Royal Mint in Kongsberg, Norway and the other five medals are cast by the Swedish Mint in Eskilstuna.

On December 10 at the Prize Award Ceremony in Stockholm, the King of Sweden hands each Laureate a diploma and a medal. The Peace Prize (diploma and medal) is presented on the same day in Oslo by the Chairman of the Norwegian Nobel Committee in the presence of the King of Norway.

The Nobel Medal for Physics and Chemistry

www.nobelprize.org

Front

Back
Glossary of Important Terms

http://www.medicinenet.com

**Amino Acid**
A group of soluble organic compounds that possess a carboxylic acid group (-COOH) and a primary amine group (-NH₂) bonded to a common carbon atom. Amino acids are the monomers of proteins.

**Apoptosis**
A form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area.

**ATP (Adenosine Triphosphate)**
The form of chemical energy that is used to fuel energy-consuming biological activities. All living organisms use ATP, though they store very little at a time. Organisms therefore produce ATP continuously through cellular respiration.

**Catalyst**
A substance that speeds up a chemical reaction but is not consumed or altered in the process.

**Chromosome**
A visible carrier of genetic information. The 3 billion base pairs in the human genome are organized into 24 distinct, physically separate microscopic units called chromosomes. All genes are arranged linearly along the chromosomes. Chromosomes contain roughly equal parts of protein and DNA; chromosomal DNA contains an average of 150 million bases. DNA molecules are among the largest molecules now known.

**Covalent Bond**
A chemical bond formed by the sharing of one or more pairs of electrons between two atoms. Covalent bonds are typically formed between two or more non-metals in molecules and giant covalent structures. The strength of the bond stems from the electron density located between the two nuclei.

**C-terminal (also known as Carboxyl-terminal residue)**
The only amino acid residue at one end of a polypeptide chain that contains a free carboxyl group.

**DNA (Deoxyribonucleic acid)**
A large nucleotide polymer having a double helical structure with complimentary bases on the two strands. Its major functions are protein synthesis and the storage and transport of genetic information.
**Enzyme**
A protein that speeds up a chemical reaction in a living organism. An enzyme acts as catalyst for specific chemical reactions, converting a specific set of reactants (called substrates) into specific products. Without enzymes, life as we know it would not exist.

**Extracellular**
Outside a cell. As opposed to **intracellular**, meaning within a cell.

**Genome**
All of the genetic information, or hereditary material, possessed by an organism.

**Hydrolysis**
A chemical reaction involving the reaction of a molecular compound with water. Covalent bonds are broken during the reaction and the elements of water are added to the chemical fragments.

**Monomer**
A small molecule, a large number of which can be polymerized via the formation of covalent bonds to form a polymer.

**Peptide**
A bond formed between the amino group of an amino acid and the carboxyl group of another (in the presence of enzymes), with the elimination of water.

**Peptide Bond**
An amide bond resulting from the condensation reaction between the amine group of one amino acid and the carboxylic acid group of another.

**Polypeptide**
A long linear chain of between 10 and 100 amino acids linked via peptide bonds.

**Polyubiquitination**
The binding of many ubiquitin molecules to the same target protein. Polyubiquitination of proteins is the triggering signal that leads to degradation of the protein in the proteasome.

**Proteasome**
A protein degradation "machine" within the cell that can digest a variety of proteins into short polypeptides and amino acids. The proteasome is itself made up of proteins. It requires ATP to work. It is hollow and has openings at both ends to allow entry of the protein to be digested.

**Substrate**
The compound acted upon by an enzyme.

**Transcription**
The process of transcribing or making a copy of genetic information stored in a DNA strand into a complementary strand of messenger RNA (mRNA) with the aid of RNA polymerases.
**Ubiquitin**
A small but extremely important protein that acts as the "kiss of death" to other proteins. Ubiquitin consists of only 76 amino acids. Ubiquitin acts as a tag by which the protein-transport machinery ferries a protein to the proteasome for degradation.

**Ubiquitination**
The "kiss of death" process for a protein. In ubiquitination, a protein is inactivated by attaching ubiquitin to it.

“We added one layer...we entered a field based on milestones that were scattered. We managed to somehow see the tip of the iceberg. There were experimental tools available to us...people laid the foundation, we added a layer, other people came on top of our layer and further distilled it and took it further – to diseases and to drug development.”

--Dr. Ciechanover, in a 2009 video interview for the Lindau Nobel Laureate Meetings
Proteins: Basic Information

By Michael Kent

Advanced Biology

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Introduction to Proteins
Proteins are large complex biological molecules which play many diverse roles in all organisms. Proteins make up a high percentage of the structure of living things (for example, about 18 percent of the human body is protein) and also take part in the fundamental processes that make up life. Every organism contains thousands of different kinds of proteins, each with its own unique three-dimensional structure which enables it to carry out a specific function. Although there are many millions of proteins, all are made from the same basic building blocks, namely approximately 20 kinds of amino acid.

Amino Acids
Amino acids are the building blocks of proteins. All amino acids have an amino group and a carboxyl group. The amino group is attached by a covalent bond to a central carbon atom called the alpha carbon. A hydrogen atom, another carbon atom, and a side chain represented by the letter R are also linked to the alpha carbon. The R group is different for each of the 20 amino acids and it determines the specific properties of a given amino acid. Two amino acids can combine to form a dipeptide by a condensation reaction between the carboxyl group of one and the amino group of the other. The resulting bond linking the two amino acids is called a peptide bond. Further amino acids can be added to either end of the dipeptide to form a polypeptide chain. Proteins consist of one of more polypeptide chains: they are polymers made up of amino acid monomers.

Protein Structure
Proteins consist of one or more chains of amino acids (polypeptide chains) folded into a unique three-dimensional shape. Simple proteins consist of amino acids only; conjugated proteins also contain a non-amino acid part called a prosthetic group. A protein’s primary structure is the sequence of amino acids that make up its polypeptide chain or chains. A protein’s secondary structure occurs when the polypeptide chain or parts of the chain either coil into an alpha-helix or fold into a beta-pleated sheet. The tertiary structure refers to the overall three-dimensional shape of a polypeptide chain. The quaternary structure refers to the way a protein’s polypeptide chains, which are chemically bonded to each other, are arranged.
**Protein Synthesis**
Proteins have many functions in the activity of a cell. The synthesis of proteins is therefore a key event. Protein synthesis consists of two phases: transcription and translation. In transcription, the information encoded in the nucleus of DNA is transferred to smaller molecules called messenger RNA (mRNA). In translation, mRNA carries this information to ribosomes in the cytoplasm, where it is used to make the polypeptides that make up a protein.

**Denaturation: Breaking down the tertiary structure**
If the bonds holding the protein in shape are broken, a process called denaturation occurs. The primary structure is retained but the polypeptide chains unravel and lose their specific shape. As a result, denatured globular proteins lose their specific function. Denaturation can occur as a result of heat, radiation, strong acids, bases and concentrated salt solutions, among other factors.

**Protein Degradation**
Protein degradation is the digestion of a protein by cellular enzymes called proteases. Regulation is necessary in both protein synthesis and protein degradation. Degradation is used by the cell for a variety of purposes, including the digestion of proteins from foods as a source of amino acids, the conversion of predecessor-proteins into their final structures, and the removal of the signal sequence of peptides after their transport through a membrane. Proteins are usually tagged for selective destruction by covalent attachment of ubiquitin, a small, compact protein that is highly conserved. However, some proteins may be degraded by proteasomes without ubiquitination.
October 6th, 2004: Technion Distinguished Professors Avram Hershko and Aaron Ciechanover have changed the world in more ways than one. Their research into the way proteins keep house at a cellular level has changed the way scientists think about the maintenance of life and health. Their research has led to new approaches to cancer, cystic fibrosis, immunological disfunction and neurodegenerative disorders. And as the first Israelis to ever win a Nobel Prize in science, the 2004 laureates of the Nobel Prize in Chemistry, are raising the torch of a new era in Israeli science.

The Unique Story of Ubiquitin
In 1975, a protein of unknown function was identified by Dr. Gideon Goldstein which he called Ubiquitin as he thought it was probably ubiquitous to all living cells – turning up everywhere in animal and plant cells and even yeast. Each living cell is made up of many tiny proteins. A protein is a molecule made up of one or more chains of amino acids in a predetermined order. Proteins maintain structure, function and regulation of cells. Each protein has its own unique function – some famous proteins being hormones, enzymes and antibodies.

While even in the 1970s protein synthesis was understood, the breakdown or destruction of unwanted proteins in cells back to amino acid was still quite a mysterious process. In the cellular picture of the cycle of life, the destruction part was not yet understood. Over two decades ago, Technion Profs. Hershko and Ciechanover were immersed in ideas as to how to complete our picture of cell regeneration through understanding how proteins are degraded.

Working closely with colleague and fellow Nobel Prize Laureate Irwin Rose, then of Fox Chase Cancer Center, Philadelphia, they showed how the small and common protein Ubiquitin attaches to other proteins, and marks them for destruction. Ubiquitin is quite a unique protein, as its task is that of a kind of runner between other proteins, labeling them if necessary for destruction or degradation. “Many knew how the body produces proteins, but not how they were destroyed,” says Hershko who is 67. “Without an engine, a car cannot run; without brakes, it is out of control. Proteins provide ways to moderate the body’s machinery.”

At first the three scientists, Hershko, graduate student Ciechanover and U.S. colleague Irwin Rose noticed that Ubiquitin had a way of binding to other proteins – but they didn’t know why.

“Hershko used a really simple system in order to make the discovery – just a soup of enzymes and proteins,” colleague John Mayer of Nottingham University told New Scientist. “From this he was able to show the target protein must be “ubiquitinated.”

Sometimes working in tandem, Ubiquitin molecules smartly seek out proteins that are no longer needed, damaged or unhelpful and tag them for degradation, escorting them to a barrel-shaped
structure called a proteasome – the cellular recycler. It is a process that cognoscenti call “ubiquitination”. It is a “kiss of death” for protein, which is a “kiss of life” for cells.

Later, the scientists identified three types of enzymes involved in the ubiquitination process. The third type – the Ubiquitin protein ligases – is the one that identifies and singles out the target protein. Ligases are the cellular whistle-blowers.

The sophisticated process takes place in cells all over the body – it is highly ubiquitous. But at first, few attached the label of “tremendous discovery” to the work. “It was a Cinderella rise from rags to riches,” recalls Mayer, “At first nobody cared about their work and those who knew something about it didn’t believe it.”

This changed as it became clear that the process of ubiquitination would allow the development of drugs against cancer and other deadly diseases: Ubiquitin’s role in destroying proteins held great promise for saving life, in fact, the role of the search and destroy protein tells part of the secret of life itself.

Nobel Prize Laureate and Chairman of the Lasker Award Jury in 2000 Dr. Joseph Goldstein lauded the Ubiquitin system as “a fundamental process that influences vital cellular events, including the cell cycle, malignant transformation, and responses to inflammation and immunity.”

“If proteins are not degraded at the right time, the cell continues to divide unchecked. This is what happens in many cancer cells… something has gone wrong in the Ubiquitin system so there is no control over cell division,” says Hershko.

“We are not a building that stays still… we are constantly exchanging our proteins, synthesizing and destroying them,” explains Ciechanover who is 57. “Some proteins get spoilt. We discovered the process by which the body exercises quality control.” Ciechanover told international media that the team’s research may “lead in the future to the development of numerous drugs for degenerative diseases and malignancies.”

Proteins build up all living things but cells constantly regenerate, divide and die, making their breakdown a vital process regulating a wide range of biological activity including preventing plants from self-pollinating – which would lead to their eventual extinction – and cell division in humans. Errors in DNA genetic code replication can cause women to miscarry or cause Down’s syndrome. Most malignant tumors have faulty DNA as a result of mistakes in cell division. Protein breakdown’s role in these processes “is absolutely fundamental,” says molecular cell biologist John Mayer, “Nothing in the cell can work without some role of Ubiquitin or its cousins.”
Proteins build up all living things: plants, animals and therefore us humans. In the past few decades biochemistry has come a long way towards explaining how the cell produces all its various proteins. But as to the breaking down of proteins, not so many researchers were interested. Aaron Ciechanover, Avram Hershko and Irwin Rose went against the stream and at the beginning of the 1980s discovered one of the cell's most important cyclical processes, regulated protein degradation.

Aaron Ciechanover, Avram Hershko and Irwin Rose have brought us to realise that the cell functions as a highly-efficient checking station where proteins are built up and broken down at a furious rate. The degradation is not indiscriminate but takes place through a process that is controlled in detail so that the proteins to be broken down at any given moment are given a molecular label, a 'kiss of death', to be dramatic. The labelled proteins are then fed into the cells' "waste disposers", the so called proteasomes, where they are chopped into small pieces and destroyed.

The label consists of a molecule called ubiquitin. This fastens to the protein to be destroyed, accompanies it to the proteasome where it is recognised as the key in a lock, and signals that a protein is on the way for disassembly. Shortly before the protein is squeezed into the proteasome, its ubiquitin label is disconnected for re-use.

Thanks to the work of the three Laureates it is now possible to understand at molecular level how the cell controls a number of central processes by breaking down certain proteins and not others. Examples of processes governed by ubiquitin-mediated protein degradation are cell division, DNA repair, quality control of newly-produced proteins, and important parts of the immune defence. When the degradation does not work correctly, we fall ill. Cervical cancer and cystic fibrosis are two examples. Knowledge of ubiquitin-mediated protein degradation offers an opportunity to develop drugs against these diseases and others.
The Ubiquitin System

By Michael Bumbulis
Associate Professor of Biology at Baldwin-Wallace College
http://homepages.bw.edu/~mbumbuli/cell/ublec/index.html

General Information
Ubiquitin (Ub) is a small protein that is composed of 76 amino acids. This protein is found only in eukaryotic organisms and is not found in either eubacteria or archaeabacteria. Among eukaryotes, ubiquitin is highly conserved, meaning that the amino acid sequence does not differ much when very different organisms are compared. For example, there are only 3 differences in the sequence when Ub from yeast is compared to human Ub. This strong sequence conservation suggests that the vast majority of amino acids that make up Ub are essential as apparently any mutations that have occurred over evolutionary history have been removed by natural selection.

Ub is a heat-stable protein that folds up into a compact globular structure. It is found throughout the cell (thus, giving rise to its name) and can exist either in free form or as part of a complex with other proteins. In the latter case, Ub is attached (conjugated) to proteins through a covalent bond between the glycine at the C-terminal end of Ub and the side chains of lysine on the proteins. Single Ub molecules can be conjugated to the lysine of these proteins, or more commonly, Ub-chains can be attached. Conjugation is a process that depends on the hydrolysis of ATP.

Ub is involved in many cell processes. For example, Ub is conjugated to the protein cycling during the G1 phase of mitosis and thus plays an important role in regulating the cell cycle. Ub conjugation is also involved in DNA repair, embryogenesis, the regulation of transcription, and apoptosis (programmed cell death)…

Ubiquitin Function
Proteins exist as a linear chain of amino acids. This chain can degrade over time as such a reaction is thermodynamically favorable in an aqueous environment (recall that proteins are synthesized by using energy to drive off a water molecule to form the peptide bond). When proteins degrade over time, this is called protein-turnover. It is the balance between a protein's degradation and its synthesis that determines the concentration of that protein inside the cell.
Studies of protein turnover rates have shown that some proteins are short-lived while others are long-lived. Long-lived proteins constitute the majority of proteins in the cell. Short-lived proteins are typically key regulatory proteins and abnormal proteins (abnormal proteins are often partially unfolded and...are prone to degradation).

Ub functions to regulate protein turnover in a cell by closely regulating the degradation of specific proteins. Such a regulatory role is very important. By regulating protein degradation, cells can quickly eliminate a protein that in turn regulates another function (like a transcription factor that is needed to express a particular gene). Furthermore, this form of control is very effective as the elimination of a particular regulatory protein ensures that the process expressed by the regulatory protein is shut-down. An alternative regulatory strategy used by cells is to simply inactivate proteins (by changing their conformation). Unlike the Ub-linked regulation, such inactivated proteins can mistakenly be reactivated. Of course, Ub-linked regulation is energetically expensive, for if a regulatory protein is needed again, it has to be re-synthesized.

Ub functions in an ATP-dependent fashion. But why is this? We don't need energy (in the form of ATP hydrolysis) to hydrolyze proteins. The reason ATP is required is because machinery is needed to specifically target the proteins that need to be degraded. *Ub itself does not degrade proteins.* It serves only as a tag that marks proteins for degradation. The degradation itself is carried out by the 26S proteasome (which we will discuss shortly). In short, proteins that are to be degraded are first tagged by conjugating them with Ub and these tagged proteins are then recognized and shuttled to the proteasome for degradation.

**The Ubiquitin-Proteasome Pathway**

If we were to mix ATP, ubiquitin, and an abnormal protein, we might expect the protein to be conjugated with Ub. But we would be wrong. Something else is needed to attach Ub to such a protein. And what is needed in most cases are three types of enzymes.

1. E1 enzymes known as Ub-activating enzymes. These enzymes modify Ub so that it is in a reactive state (making it likely that the C-terminal glycine on Ub will react with the lysine side-chains on the substrate protein).

2. E2 enzymes known as Ub-conjugating enzymes. These enzymes actually catalyze the attachment of Ub to the substrate protein.

3. E3 enzymes known as Ub-ligases. E3’s usually function in concert with E2 enzymes, but they are thought to play a role in recognizing the substrate protein.
In yeast, there are many types of E1, E2, and E3 enzymes. For example, 13 different E2 enzymes have been found. While they all carry out the conjugation reaction, they are apparently tailored for specific functions. For example, Ubc2 is an E2 enzyme that works in DNA repair, while Ubc3 is also an E2 enzyme that functions to degrade cycling as part of the cell-cycle.

The general reaction pathway is shown in the figure below. First, Ub is activated by E1 in an ATP-dependent fashion. E2 and E3 then work together to recognize the substrate protein and conjugate Ub to it. Ub can be attached as a monomer or as a previously synthesized chain...From this point, the ubiquinated protein is shuttled to the proteasome for degradation.

How does ubiquitination lead to protein degradation?
Recall that Ub does not itself degrade proteins and instead merely tags proteins for degradation. But it is not entirely accurate to think of Ub as a simple tag, as Ub does appear to be involved in degradation. The proteasome is the structure that actually does the degrading. Ubiquitin's degradation role may simply be to decrease the rate of dissociation between proteasomes and interacting substrate proteins. That is, without Ub, proteins may interact with the proteasome, but quickly dissociate. Ub slows down this dissociation. A substrate protein that is conjugated with Ub-chains is thought to interact with a proteasome for a longer period of time, thus increasing the likelihood that the proteasome will degrade it...In fact, Ub could actually function to tether the substrate protein to the proteasome.

Deubiquitination: Another layer of complexity
As if things were not complex enough, there also exists a class of enzymes that function to remove Ub from substrate proteins, thus rescuing them from degradation. There are many types of deubiquitinating enzymes and these are currently being explored. This clearly represents yet one more means of regulating the concentration of proteins in a cell. That is, ubiquitinated proteins could be deubiquinated prior to their association with the proteasome, allowing for fine-tuning in concentration regulation. Thus, for a protein to be degraded, not only must it have some type of signal that results in Ub-conjugation, but it must also escape the deubiquinating enzymes. Clearly the cell invests much activity to prevent indiscriminate protein degradation.
A human cell contains some hundred thousand different proteins. These have numerous important functions: as accelerators of chemical reactions in the form of enzymes, as signal substances in the form of hormones, as important actors in the immune defense and by being responsible for the cell's form and structure. This year's Nobel Laureates in chemistry, Aaron Ciechanover, Avram Hershko and Irwin Rose, have contributed ground-breaking chemical knowledge of how the cell can regulate the presence of a certain protein by marking unwanted proteins with a label consisting of the polypeptide ubiquitin. Proteins so labeled are then broken down – degraded – rapidly in cellular "waste disposers" called proteasomes.

Through their discovery of this protein-regulating system Aaron Ciechanover, Avram Hershko and Irwin Rose have made it possible to understand at molecular level how the cell controls a number of very important biochemical processes such as the cell cycle, DNA repair, gene transcription and quality control of newly-produced proteins. New knowledge of this form of controlled protein death has also contributed to explaining how the immune defense functions. Defects in the system can lead to various diseases including some types of cancer.

Degradation needs no energy – or does it?
While great attention and much research have been spent on understanding how the cell controls the synthesis of a certain protein – at least five Nobel Prizes have been awarded in this area – the reverse, the degradation of proteins, has long been considered less important. A number of simple protein-degrading enzymes were already known. One example is trypsin, which in the small intestine breaks down proteins in our food to amino acids. Likewise, a type of cell organelle, the lysosome, in which proteins absorbed from outside are broken down, had long been studied. Common to these processes is that they do not require energy in order to function.

Experiments as long ago as the 1950s showed, however, that the breakdown of the cell's own proteins does require energy. This long puzzled researchers, and it is precisely this paradox that underlies this year's Nobel Prize in Chemistry: that the breakdown of proteins within the cell requires energy while other protein degradation takes place without added energy. A first step towards an explanation of this energy-dependent protein degradation was taken by Goldberg and his co-workers who in 1977 produced a cell-free extract from immature red blood cells, reticulocytes, which catalyse the breakdown of abnormal proteins in an ATP-dependent manner (ATP = adenosine triphosphate – the cell's energy currency).

Using such an extract Aaron Ciechanover, Avram Hershko and Irwin Rose, in a series of epoch-making biochemical studies in the late 1970s and early 1980s, succeeded in showing that protein degradation in cells takes place in a series of step-wise reactions that result in the proteins to be destroyed being labeled with the polypeptide ubiquitin. This process enables the cell to break down unwanted proteins with high specificity, and it is this regulation that requires energy… Much of the work was done during a series of sabbatical leaves that Avram Hershko and Aaron
The Echo Foundation  93  The Aaron Ciechanover Project

Ciechanover of the Technion (Israel Institute of Technology) spent with Irwin Rose at the Fox Chase Cancer Center in Philadelphia, USA.

The label is ubiquitin
The molecule that would later prove to be the label that marks out a protein for degradation was isolated as early as 1975. This 76-amino-acid-long polypeptide was isolated from calf sweetbread and was assumed to participate in the maturation of white blood cells. Since the molecule was subsequently found in numerous different tissues and organisms – but not in bacteria – it was given the name ubiquitin (from Latin *ubique*, "everywhere") (fig. 1).

The discovery of ubiquitin-mediated protein degradation
After taking his doctorate, Avram Hershko had studied energy-dependent protein degradation in liver cells, but decided in 1977 to transfer to the reticulocyte extract described above. This extract contained large quantities of haemoglobin, which upset the experiments. In their attempts to remove the haemoglobin using chromatography, Aaron Ciechanover and Avram Hershko discovered that the extract could be divided into two fractions, each inactive on its own. But it turned out that as soon as the two fractions were recombined, the ATP-dependent protein degradation restarted. In 1978 the researchers reported that the active component of one fraction was a heat-stable polypeptide with a molecular weight of only 9000 which they termed APF-1 (active principle in fraction 1). This protein later proved to be ubiquitin.

The decisive breakthrough in the research was reported in two works that Ciechanover, Hershko and Rose published in 1980. Until that time the function of APF-1 was entirely unknown. In the first work it was shown that APF-1 was bound covalently, i.e. with a very stable chemical bond, to various proteins in the extract.

In the second work it was further shown that many APF-1 molecules could be bound to the same target protein; the latter phenomenon was termed polyubiquitination. We now know that this polyubiquitination of substrate proteins is the triggering signal that leads to degradation of the protein in the proteasome. It is this reaction that constitutes the actual labelling, the "kiss of death" if you will.

At a stroke, these entirely unanticipated discoveries changed the conditions for future work: it now became possible to concentrate on identifying the enzyme system that binds ubiquitin to its target proteins. Since ubiquitin occurs so generally in various tissues and organisms, it was quickly realised that ubiquitin-mediated protein degradation must be of general significance for the cell. In addition, the researchers guessed that the energy requirement in the form of ATP enabled the cell to control the specificity of the process.

The field was now open and between 1981 and 1983 Ciechanover, Hershko, Rose and their post docs and students developed "the multistep ubiquitin-tagging hypothesis" based on three newly-
discovered enzyme activities they termed E1, E2 and E3. We now know that a typical mammalian cell contains one or a few different E1 enzymes, some tens of E2 enzymes and several hundred different E3 enzymes. It is the specificity of the E3 enzyme that determines which proteins in the cell are to be marked for destruction in the proteasomes.

All the studies up to this point had been done in cell-free systems. To be able to study the physiological function of ubiquitin-mediated protein degradation as well, Avram Hershko and his co-workers developed an immunochemical method. By using antibodies to ubiquitin, ubiquitin-protein-conjugate could be isolated from cells where the cell proteins had been pulse-labeled with a radioactive amino acid not present in ubiquitin. The results showed that cells really break down faulty proteins using the ubiquitin system, and we now know that up to 30% of the newly-synthesized proteins in a cell are broken down via the proteasomes since they do not pass the cell's rigorous quality control.

The proteasome – the cell's waste disposer
What is a proteasome? A human cell contains about 30,000 proteasomes: these barrel-formed structures can break down practically all proteins to 7-9-amino-acid-long peptides. The active surface of the proteasome is within the barrel where it is shielded from the rest of the cell. The only way in to the active surface is via the "lock", which recognizes polyubiquitinated proteins, denatures them with ATP energy and admits them to the barrel for disassembly once the ubiquitin label has been removed. The peptides formed are released from the other end of the proteasome. Thus the proteasome itself cannot choose proteins; it is chiefly the E3 enzyme that does this by ubiquitin-labelling the right protein for breakdown (fig. 3).

More recent research
While the biochemical mechanisms underlying ubiquitin-labelled protein degradation were laid bare around 1983 its physiological significance had not yet been fully understood. That it is of importance in destroying defective intracellular proteins was known but, to proceed, a mutated cell was needed in the ubiquitin system. By studying in detail how the mutated cell differs from a normal cell under various growth conditions, it was hoped to gain a better idea of what reactions in the cell depend on the ubiquitin system.

A mutated mouse cell had been isolated in 1980 by a research group in Tokyo. Their mouse-cell mutant contained a protein that, because of the mutation, was sensitive to temperature. At lower temperatures the protein functioned as it should, but not at higher. Cells cultured at the higher temperature stopped growing. In addition, they showed defective DNA synthesis and other erroneous functions at the higher temperature. Researchers in Boston quickly showed that the heat-sensitive protein in the mutant mouse cell was the ubiquitin-activating enzyme E1. Obviously, ubiquitin activation was necessary for the cell to function and reproduce itself at all. Controlled protein breakdown was not only important for degrading incorrect proteins in the cell.

Fig 3. The cell's waste disposer, the proteasome. The black spots indicate active, protein-degrading surfaces.
but it probably also took part in control of the cell cycle, DNA replication and chromosome structure.

Since the late 1980s a number of physiologically important substrates for ubiquitin-mediated protein breakdown have been identified. Only a few of the most important will be mentioned here.

**DNA repair, cancer and programmed cell death**

Protein p53 has been dubbed "the guardian of the genome" and it is a tumour-suppressor gene. This means that as long as a cell can produce p53 the development of cancer is hampered. Sure enough, the protein is mutated in at least 50% of all human cancer. The amount of protein p53 in a normal cell is low in consequence of continual production and breakdown. The breakdown is regulated through ubiquitination and the E3 enzyme responsible forms a complex with protein p53. Following DNA injury, protein p53 is phosphorylated and can no longer bind to its E3 enzyme. The breakdown stops and the quantity of p53 in the cell rises rapidly. Protein p53 acts as a transcription factor, i.e. a protein that controls the expression of a certain gene. Protein p53 binds to and controls genes that regulate DNA repair and programmed cell death. Raised levels of protein p53 lead first to interruption of the cell cycle to allow time for repair of DNA damage. If the damage is too extensive the cell triggers programmed cell death and "commits suicide".

Infection with human papilloma virus correlates strongly to the occurrence of cervical cancer. The virus avoids the protein p53 control function through one of its proteins activating and changing the recognition pattern of a certain cellular E3 enzyme, E6-AP, which is tricked into ubiquitinating the protein p53, which is totally destroyed. In consequence of this the infected cell can no longer repair DNA damage in a normal manner or trigger programmed cell death. The DNA mutations increase in number and this can ultimately lead to the development of cancer.

**Immune and inflammatory reactions**

A certain transcription factor regulates many of the genes in the cell that are important for immune defence and inflammatory reactions. This protein, the transcription factor, occurs bound to an inhibitor protein in the cytoplasm of the cell, and the bound form of the transcription factor lacks activity. When cells are exposed to bacteria or various signal substances, the inhibitor protein is phosphorylated, and this results in its being ubiquitinated and broken down in the proteasome. The released transcription factor is transported to the cell nucleus where it binds to, and activates the expression of, specific genes.

The ubiquitin-proteasome system also produces the peptides that are presented by the immune defence on the surface of a virus-infected cell by breaking down virus proteins to suitable sizes. T lymphocytes recognise these peptides and attack the cell as an important part of our defence against virus infections.

**Cystic fibrosis**

The hereditary disease cystic fibrosis, CF, is caused by a non-functioning plasma membrane chloride channel called CFTR, the "cystic fibrosis transmembrane conductance regulator". Most CF patients have one and the same genetic damage, loss of the amino acid phenylalanine in the CFTR protein. The mutation causes faulty folding of the protein and this in turn leads to the
protein being retained in the cell's control system for protein quality. This system ensures that the incorrectly folded protein is destroyed through ubiquitin-mediated protein breakdown instead of being transported out to the cell wall. A cell with no functioning chloride channel can no longer transport chloride ions through its wall. This affects secretion in, among other organs, the lungs and leads to the accretion of thick phlegm in the lungs which impairs their function, greatly increasing the risk of infection.

Regulation of the cell cycle
When a cell is to make a copy of itself, many chemical reactions are involved. In a human being, six thousand million base pairs must be duplicated in DNA. These are gathered in 23 chromosome pairs that must be copied. Ordinary cell division, mitosis, and the formation of sex cells, meiosis, have many points of contact with the subjects of this year's Nobel Prize. The E3 enzyme responsible, a protein complex termed the "anaphase-promoting complex" (APC) checks that the cell goes out of mitosis. This enzyme complex has also proved to play an important role in the separation of the chromosomes during mitosis and meiosis. A different protein complex acts like a rope around the chromosome pair, holding it together. At a given signal, the APC labels an inhibitor of a certain protein-degrading enzyme, whereupon the inhibitor is carried to the proteasome and destroyed. The enzyme is released, is activated and cuts the rope around the chromosome pair. Once the rope is gone, the chromosome pair can be separated. Incorrect chromosome division during meiosis is the commonest cause of spontaneous miscarriage during pregnancy, and an extra chromosome 21 in humans leads to Down's syndrome. Most malignant tumours have cells with changed numbers of chromosomes as a result of incorrect chromosome division during mitosis.

The ubiquitin system has become an interesting area of research for medicines against various diseases. Such preparations can be aimed at components of the ubiquitin-mediated breakdown system to prevent the degradation of specific proteins. They can also be designed to cause the system to destroy unwanted proteins.

This year's Laureates have explained the molecular background to a protein regulation system of great importance for all higher cells. New cell functions controlled by ubiquitin-mediated protein degradation are being discovered all the time and this research is being conducted in numerous laboratories all over the world.
In an exclusive interview, Neurology Today spoke to Nobelist Aaron Ciechanover and other experts in the field about the impact his discovery of ubiquitin-mediated protein degradation has had on understanding neurologic diseases and potential therapeutic targets.

NEW YORK CITY - In cities and towns across the nation, we take our garbage collectors for granted - they stop by late at night or early in the morning when most of us are asleep, and most of us have little idea where they take their full trucks.

The same disregard for cellular garbage existed for many years among researchers who studied proteins when Aaron Ciechanover, PhD, began working on the problem as a graduate student in the late 1970s, he told a crowded auditorium here in a lecture at Columbia University in April. But the fundamental biochemistry of cellular garbage disposal is now bringing new insights to a host of neurological diseases and may lead to novel therapies.

Last October, Dr. Ciechanover and Avram Hershko, MD, PhD, both from Technion University in Haifa, Israel, and Irwin Rose, PhD, of the University of California-Irvine, were awarded the Nobel Prize in Chemistry for their discovery 30 years ago of ubiquitin-mediated protein degradation - a mechanism found in every living cell, targeting damaged or used proteins, but not the active ones.

A cell achieves a delicate state of equilibrium by existing in a constant state of flux, synthesizing and destroying proteins at a hefty turnover rate of 5 percent per day. On top of simply removing cellular trash, the ubiquitin system acts as a control gauge for crucial cell processes such as cell division, DNA repair, and aspects of the immune system by rapidly clearing away specific proteins. Destruction is a form of regulation, Dr. Ciechanover explained.

Ubiquitin: Two-Stage Process
Protein destruction via ubiquitin is a two-stage process. First, ubiquitin molecules, which act as tagging units, bind to the target proteins forming a chain - a process that biochemists have dramatically termed the kiss of death. This poly-ubiquitin chain is then recognized by a molecular complex called the proteasome - essentially a mill that breaks down the tagged protein into short segments of amino acids that can then be recycled for further protein synthesis.

It's like a court process, Dr. Ciechanover explained. Initially, you indict the person for wrongdoing, or in this case malfunctioning, and then you execute him.

In the years since its discovery, the ubiquitin-mediated pathway has become one of the biggest fields in biology. Researchers studying proteins involved in everything from cancer to cystic fibrosis to Down syndrome simply began bumping into it, Dr. Ciechanover told Neurology
Today. People didn't walk into the ubiquitin field because they chose to work on degradation. They worked on their own proteins, but each one discovered that their favorite protein was short-lived.

A Common Disease Pathology
Seven years ago, scientists first linked the neurodegenerative condition spinocerebellar ataxia to an inability of the ubiquitin system to clear a mutated protein called ataxin-1. Since then, associations between the ubiquitin system and disease pathology have either been shown or suspected in a long list of neurodegenerative disorders that includes Parkinson disease, Alzheimer disease, Huntington disease, amyotrophic lateral sclerosis, and prion diseases. These conditions have varying - and in many cases poorly understood - etiologies, but what unites them, is that they all show accumulation of clumps in the CNS made up of misfolded proteins, a pattern suggesting problems in the disposal of intracellular garbage.

Although some commonality was long suspected, it is now known what the similarity is, says Patrik Brundin, MD, PhD, Professor of Neuroscience at Lund University in Sweden. I would say that's a major paradigm shift.

What's trickier still is determining ubiquitin's role in disease pathology. Is the cell's machinery for disposing of these proteins broken, or does the problem lie in the proteins themselves, with a still-unknown deficit causing them to accumulate and to gum up the degradation system?

Differentiating these two possibilities would shed much-needed light on the pathology of these diseases, says Huda Y. Zoghbi, MD, a Howard Hughes Medical Institute Investigator in Molecular Genetics at the Baylor College of Medicine in Houston. Her team bred mice with spinocerebellar ataxia with a special mutant in which ubiquitin molecules are labeled with a fluorescent marker, allowing researchers to observe when and how the misfolded proteins accumulate.

They found that the mice developed symptoms of the disease long before problems in the ubiquitin pathway were evident. That is good news, Dr. Zoghbi said. Since the machinery seems to be intact, at least early in the disease, it means if we can just reduce the protein load we can help these patients.

But others have found evidence for the opposite hypothesis. You look at isolated studies, and they're all good, says George N. DeMartino, PhD, Professor of Physiology at the Southwestern Medical Center at the University of Texas, who collaborated with Dr. Zoghbi on the study. But you get these contradicting theories.

The Path to New Therapies
A clearer understanding of ubiquitin's role in neurodegenerative diseases will undoubtedly lead to new medicines, researchers say. We need to look at the ubiquitin system not only as a problem, but as an opportunity, said Nico P. Dantuma, PhD, Senior Scientist in Cell and Molecular Biology at the Karolinska Institute in Sweden. Even if it's not the bad guy, we can still target it therapeutically to make it more efficient.
Already, biochemistry has yielded one powerful new medicine called bortezomib (Velcade), which was approved by the US Food and Drug Administration in 2003 to treat multiple myeloma, a lymphoproliferative disease. Bortezomib inhibits the proteasome and probably kills cancer cells indirectly, by preventing the breakdown of proteins that suppress the cancer cells' growth.

But bortezomib highlights two major challenges in developing treatments based on the ubiquitin-mediated pathway. First, Dr. Ciechanover told Neurology Today, developing ubiquitin system-based drugs to treat neurological diseases is simply a more difficult pharmaceutical problem than developing drugs that treat cancer. Administering a small molecule like bortezomib is the biochemical equivalent of throwing a spanner in the works - it slows down the cell's normal degradation process by physically blocking enzymes from interacting with each other. But it is not clear what a drug would have to do to get the process to speed up.

Second, drugs that interfere with such a ubiquitous biochemical process are likely to have strong side effects. In fact, researchers have been surprised that bortezomib works so well, and point out that the long-term side effects are still unknown. There's nobody around who has used [it] for more than a few years, said Dr. DeMartino.

It may be possible to rev the system up just a little bit, not enough to be toxic, says Dr. Zoghbi, but more disease-specific approaches will also needed - and that will require a better understanding of the basic biology of each one. In Parkinson disease, we don't even know what protein is accumulating, she said.

Meanwhile, researchers in industry and academia are screening for drugs that will act not on the ubiquitin system, but on the misfolded proteins themselves. Molecules called chaperones, which help proteins take their correct three-dimensional shape, are the most promising candidates. In cell culture, if you over-express certain kinds of chaperones, you really can prevent aggregation, says Dr. DeMartino. It may be possible to find a molecule that boosts their production or to synthesize molecules, which mimic the way they lend a helping hand.
What is Parkinson’s disease?

From the National Parkinson Foundation (www.parkinson.org)

Parkinson’s disease (PD) is a neurodegenerative brain disorder that progresses slowly in most people. What this means is that individuals with PD will be living with PD for twenty years or more from the time of diagnosis. However, having PD does not mean you cannot have a good quality of life. Because there is no cure, your doctors will be focused and dedicated to finding treatments that help control the symptoms of PD and enable you to manage your PD.

Normally, there are brain cells (neurons) in the human brain that produce dopamine. These neurons concentrate in a particular area of the brain, called the substantia nigra. Dopamine is a chemical that relays messages between the substantia nigra and other parts of the brain to control movements of the human body. Dopamine helps humans to have smooth coordinated muscle movements. When approximately 60 to 80% of the dopamine-producing cells are damaged, and do not produce enough dopamine, the motor symptoms of Parkinson’s disease appear. This process of impairment of brain cells is called neurodegeneration.

The current theory (so-called Braak’s hypothesis) is that the earliest signs of Parkinson’s are found in the enteric nervous system, the medulla and in particular, the olfactory bulb, which controls your sense of smell. Under this theory, Parkinson’s only progresses to the substantia nigra and cortex over the years. This theory is increasingly borne out by evidence that non-motor symptoms, such as a loss of sense of smell, hyposmia, sleep disorders and constipation may precede the motor features of the disease by several years. For this reason, researchers are increasingly focused on these “non-motor” symptoms to both detect PD as early as possible and to look for ways to stop its progression.

Famous People With Parkinson's Disease
(source: www.discoveryhealth.com)

Michael J. Fox -- Canadian film and television actor
Muhammad Ali -- three-time World Heavyweight Boxing Champion
Billy Graham -- televangelist
Janet Reno -- former Attorney General
Katharine Hepburn -- stage and screen actress (deceased)
Harry S. Truman -- 33rd U.S. President (deceased)
The following is one example of the research that has been funded in recent years by the National Parkinson foundation to determine the link between ubiquitin and Parkinson’s disease.

**Analysis of Parkin-Mediated Ubiquitination by Quantitative Mass Spectrometry**
Edward A. Fon, M.D.
McGill University, FY 2008 Grant

Parkinson's disease (PD) involves the death of dopamine neurons and leads to devastating motor and functional impairment. Important advances have been made using molecular and genetic approaches and in the past years, several genes have been identified, which cause familial forms of PD. Of these genes, parkin accounts for a large proportion of cases...Parkin is a key enzyme in the ubiquitin system. It functions by attaching the small protein ubiquitin onto other proteins, thereby changing the properties or promoting the destruction of the tagged proteins. Loss of parkin activity is believed to result in the death of susceptible neurons. Remarkably, the majority of parkin point mutations do not abolish parkin activity. How then do they lead to disease? We believe that many of the parkin mutations change the types of linkages that attach ubiquitin onto target proteins. As the type of ubiquitin attachments may alter the fate and function of the tagged protein, we propose that such changes may explain how most parkin mutations lead to PD. However, until recently, it has not been possible to accurately assess the types of ubiquitin attachments. We will use Absolute Quantification of Ub (AQUA), a novel mass spectrometry technique, to characterize how parkin attaches ubiquitin onto target proteins. As altering the ubiquitin linkages can impact the function of both parkin and its substrates, the finding would have major implication for PD pathogenesis. Ultimately, the hope is that characterizing such fundamental aspects of parkin function will point towards better treatments, and possibly a cure for PD.
What is Alzheimer’s Disease?

From the Alzheimer’s Association (www.alz.org)

Introduction
Alzheimer’s disease is a brain disorder named for German physician Alois Alzheimer, who first described it in 1906. Scientists have learned a great deal about Alzheimer’s disease in the century since Dr. Alzheimer first drew attention to it. Today we know that Alzheimer’s:

• **Is a progressive and fatal brain disease.** As many as 5.3 million Americans are living with Alzheimer’s disease. Alzheimer's destroys brain cells, causing memory loss and problems with thinking and behavior severe enough to affect work, lifelong hobbies or social life. Alzheimer’s gets worse over time, and it is fatal. Today it is the seventh-leading cause of death in the United States.

• **Is the most common form of dementia,** a general term for memory loss and other intellectual abilities serious enough to interfere with daily life. Alzheimer’s disease accounts for 50 to 80 percent of dementia cases.

• **Has no current cure.** But treatments for symptoms, combined with the right services and support, can make life better for the millions of Americans living with Alzheimer’s. There is an accelerating worldwide effort under way to find better ways to treat the disease, delay its onset, or prevent it from developing.

Alzheimer's and the brain
Just like the rest of our bodies, our brains change as we age. Most of us notice some slowed thinking and occasional problems with remembering certain things. However, serious memory loss, confusion and other major changes in the way our minds work are not a normal part of aging. They may be a sign that brain cells are failing.

The brain has 100 billion nerve cells (neurons). Each nerve cell communicates with many others to form networks. Nerve cell networks have special jobs. Some are involved in thinking, learning and remembering. Others help us see, hear and smell. Still others tell our muscles when to move. In Alzheimer’s disease, as in other types of dementia, increasing numbers of brain cells deteriorate and die.

The role of plaques and tangles
Two abnormal structures called plaques and tangles are prime suspects in damaging and killing nerve cells. Plaques and tangles were among the abnormalities that Dr. Alois Alzheimer saw in the brain of [his patient], although he called them different names.

• **Plaques** build up between nerve cells. They contain deposits of a protein fragment called beta-amyloid. Tangles are twisted fibers of another protein called tau (rhymes with “wow”).
• **Tangles** form inside dying cells. Though most people develop some plaques and tangles as they age, those with Alzheimer’s tend to develop far more. The plaques and tangles tend to form in a predictable pattern, beginning in areas important in learning and memory and then spreading to other regions.

Scientists are not absolutely sure what role plaques and tangles play in Alzheimer’s disease. Most experts believe they somehow block communication among nerve cells and disrupt activities that cells need to survive.

Alzheimer’s disease leads to nerve cell death and tissue loss throughout the brain. Over time, the brain shrinks dramatically, affecting nearly all its functions. Photo courtesy of the Alzheimer’s Association.
Brain enzyme treatment relieves memory lapse in Alzheimer's mice

By Heidi Hardman
Cell Press
August 24, 2006

An enzyme that helps neurons rid themselves of excess or aberrant proteins is required for normal brain function, according to a new report in the August 25, 2006 issue of the journal Cell, published by Cell Press. What's more, by increasing brain levels of the enzyme in mice with Alzheimer's symptoms, the researchers found they could reverse lapses of memory characteristic of the debilitating disease.

Treatments that elevate the protein, known as ubiquitin C-terminal hydrolase L1 (Uch-L1), might therefore have potential as a new therapy for Alzheimer's disease, according to the researchers. Currently available therapies have almost exclusively targeted amyloid beta (Aβ), the protein responsible for the "amyloid plaques" that riddle the brains of patients with Alzheimer's disease, they added.

"By injecting what is essentially a Uch-L1 drug to raise its levels in the brain, we were able to restore a great deal of brain activity in a transgenic mouse model of Alzheimer's disease," said Michael Shelanski of Columbia University.

"While amyloid beta is certainly a key player in Alzheimer's disease--and efforts to reduce it remain a worthy goal--our results show that, even in the presence of the plaque, damage to memory can be reversed."

The findings suggest that neurons' protein-ridding machinery, the so-called ubiquitin/proteasomal pathway, may play an important early role in the pathogenesis of Alzheimer's disease, he added.

Ubiquitin is a "tag" that marks proteins for destruction by the cellular "garbage disposal" known as the proteasome, Shelanski explained. Uch-L1 acts as the proteasome's "gatekeeper," he added. Before proteins can be eliminated by the proteasome, Uch-L1 must remove their ubiquitin tag. Earlier studies found that the brains of Alzheimer's disease patients show an accumulation of ubiquitin-tagged proteins, suggesting some defect of the protein degradation machinery, the researchers noted. Studies of the brains of humans with Alzheimer's after death found evidence that the proteasome remained intact but largely unable to degrade proteins.

Interestingly, Uch-L1--a protein found almost exclusively in nerve cells--was also found at reduced levels in the Alzheimer's brain. Unpublished studies by Shelanski's group found that cells treated with Aβ exhibited a rapid drop in Uch-L1, he said.

To further investigate in the current study, the researchers treated brain slices with a chemical that blocks Uch-L1 function. The treated brain tissue displayed a decline in "long-term
potentiation" (LTP), a process whereby nerve connections are strengthened. LTP is regarded as the cellular basis for learning and memory.

Treatments that restored Uch-L1 levels corrected deficits in nerve transmission both in brain slices treated with Aβ and in slices taken from transgenic mice with mutations that lead to elevated Aβ and associated cognitive decline.

The researchers next asked whether Uch-L1 played an important role in fear conditioning, a form of learning known to be impaired in several mouse models of Alzheimer's disease.

For fear conditioning, mice treated with the Uch-L1 inhibitor and control mice were placed in a novel context (a fear-conditioning box) and exposed to a tone paired with a mild foot shock. Their ability to learn fear was tested 24 hr later by measuring "freezing" behavior in response to the box or the auditory cue. Contextual versus cued responses represent different forms of learning that depend on different parts of the brain.

A day after their exposure to the shock, mice with reduced levels of Uch-L1 showed a decrease in freezing behavior to 65% that of normal mice when placed in the box. The differences between treated and untreated mice persisted 7, 14, and 21 days after exposure to the electric shock, they reported.

On the other hand, the mice showed no differences in response to the auditory tone, suggesting variation among brain regions in the role of Uch-L1.

In mice with symptoms that mimic those found in patients with Alzheimer's disease, treatments that raised Uch-L1 greatly increased their freezing time compared to their transgenic littermates when contextual learning was assessed over time, the researchers found. Improvements in the treated animals' ability to establish a memory for fear did not depend on changes in Aβ levels. The findings provide a new window into the Alzheimer's brain that could lead to new therapies, the researchers said.

"The rapid fall in Uch-L1 activity in response to Aβ raises the possibility that, in the Alzheimer's brain, Aβ initiates a signaling cascade that results in the partial inhibition of proteasome activity more rapidly than is likely as the result of the accumulation of misfolded or undigestable proteins."

"Our data suggest that Uch-L1 could be an attractive target for the development of new therapeutic approaches to Alzheimer's disease, either alone or in combination with therapies that alter Aβ levels."
The Ubiquitin Proteasome System -
Out of STEP in AD?

By Tom Fagan
Alzheimer’s Research Forum
April 30, 2010

You might be inclined to wonder about your refuse collector if garbage was piling up in your neighborhood. What about in your brain? For years scientist have looked to cellular recycling mechanisms to explain the accrual of toxic protein aggregates, such as the senile plaques and neurofibrillary tangles found in Alzheimer’s disease (AD), or the Lewy bodies found in Parkinson's. Two papers in this week's Journal of Neuroscience may bring us a few steps closer to understanding the relationship between the cell's protein recycling machinery—the ubiquitin proteasome system—and AD.

Led by Paul Lombroso at Yale University, New Haven, Connecticut, researchers report that a protein phosphatase accumulates in mouse models of AD and mediates Amyloid beta (Aβ) toxicity. The buildup of the phosphatase, called striatal-enriched protein tyrosine phosphatase 61—or STEP61—is not due to overproduction, but failure of degradation by the ubiquitin proteasome system (UPS), the researchers show. In a second paper, a group led by Andrea LeBlanc at McGill University, Montreal, Canada, report that a ubiquitin-dependent ATPase that is crucial for the UPS is cleaved by caspase-6, a protease that LeBlanc's research implicates in AD pathology. One cleavage fragment of the ATPase acts as an inhibitor of the UPS in cells, and the researchers show that this fragment is elevated in AD brains, hinting that it might impair the UPS in the disease as well. "The papers agree with the idea that an efficient working UPS is very relevant for preventing and/or delaying AD," suggested Fred van Leeuwen, University of Maastricht, in an email to ARF.
Discovery of Ubiquitin-Mediated Protein Degradation

Chapter Study Questions

1. What factors do you think should be of highest importance in the awarding of a Nobel Prize for science? How could these particular factors be determined and enforced? (For example, if you believe the potential benefit to mankind is an important factor, how could you “rate” the benefit when comparing discoveries?)

2. Some discoveries can be both beneficial and harmful to humans. For example, radiation helps us cure cancer but can also cause cancer. Should the Nobel Prize committees consider possible harm or misuse of a discovery when considering to whom to award the Nobel Prize?

3. In your own words, define the term polyubiquitination.

4. In your own words, explain the Ubiquitin Proteasome Pathway step by step.

5. Velcade (Bortezomib), the drug approved in 2003 for the treatment of multiple myeloma, has not been in use long enough for its long-term side effects to be known. Would you consider using this drug if you needed it, not knowing the long-term side effects? Why or why not?

6. Millions of dollars are donated for scientific research every year. Do you think that there is currently enough research being done on Ubiquitin-related diseases, such as Alzheimer’s and Parkinson’s? In your opinion, what can be done to accelerate research on the cures for neurodegenerative diseases?

7. Discussions concerning the direction and role of scientific research frequently center on the question of basic research versus applied research. To roughly define these terms we can think of basic research as being “curiosity and question driven,” while applied research is more “demand or problem driven,” sometimes with a commercial application. Which type of research do you think is more important?

8. In light of what you have learned about Dr. Ciechanover and his work, how might you argue for supporting basic research to those who propose that the majority of research funding should go primarily to those areas that have a direct application?
V. Current Work at the Technion

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“I’d always looked to me an open field. I don’t know. I have this exploratory character. I need something that has dimensions beyond my life and beyond my horizons. I cannot see myself doing something that has a solution. That I finish it and go on to the next one. I need an unlimited field of questions, and that I will never be able to see beyond it. The questions will keep on popping. And nature certainly provided it for me.”

--Dr. Ciechanover, excerpted from a 2006 video interview with the Vega Science Trust
History of the Technion

From the Technion official website

"Israel can win the battle for survival only by developing expert knowledge in technology."
Prof. Albert Einstein, President of the first Technion Society

"Technion has a great contribution to make to Israel's future prosperity, and Israel's prosperity cannot but be of great benefit to other countries, as well."
Winston Churchill, the late Prime Minister of Great Britain

The Technion
As Israel's oldest and premier institute of science and technology, the Technion-Israel Institute of Technology has been an active and leading participant in Israel's establishment and development. With supreme effort and unyielding dedication, deserts have bloomed, swamps have been transformed into fertile agricultural valleys, and sand has given way to silicon. Israel is now recognized as one of the world's most prominent high-tech innovators, and has been called the second Silicon Valley.

Technion Graduates
71,000 graduates over the past three-quarters of a century have been one of the single most substantial forces propelling the country forward, committed to ensuring a bright and prosperous future.

- Technion scientists are world renowned for their expertise in research and development of technologies related to the fields of water, soil and food engineering, and infrastructures.
- Scientists and engineers alike are flourishing in the myriad high-tech industrial parks that dot Israel's urban landscapes.
- Researchers in the medical field are trailblazing novel drugs and therapies on their quest to cure life-threatening diseases.
**Unforgettable Decades:**

**1920s - Founding the Future**

After some years of intense pioneering activities, with Prof. Albert Einstein's deep involvement, the Technion opened its doors in 1924, becoming Israel’s first modern university.

The first undergraduate class consisted of 16 students in two areas of instruction: Civil Engineering and Architecture.

After serious debate, the language of instruction was chosen to be Hebrew, as opposed to German.

The impact of the first Jewish university in an embryonic Jewish state brought about a vital link between the two.

**1930s - Charting the Unknown**

In the 1930s, the Institute absorbed large numbers of Jewish students and distinguished scholars from Poland, Germany and Austria, who were fleeing the Nazi regime.

By the late 1930s the demand for technical university graduates had increased. Enrollment exceeded 400 students, and the University had expanded to include a degree in industrial engineering, 11 labs and a nautical school.

**1940s – Citizen of the World**

In the years preceding the establishment of the State, Technion was an active center for the Jewish underground and a source of technological defense solutions crucial to the struggle for independence.

In 1948, with a student body of 680, Technion celebrated Israel's Declaration of Independence.

The developing state created new demands on the veteran university. To meet these needs, Technion launched a variety of ambitious projects, including the establishment of the Department of Aeronautical Engineering in 1949, which laid the foundation for Israel’s successful aerospace industries and insurmountable Air Force.
From electricity to telephone networks, from founding industries to producing rapid housing to meet the demands of immigration, Technion was the powerhouse behind the evolution of the state.

1950s - A Move Uphill

This decade ushered in an era of expansion for the Technion. When the original campus in central Haifa became too small, Prime Minister David Ben-Gurion selected a 300-acre site on Mount Carmel for a new campus. In 1953, the Institute began its move to Technion City on Mount Carmel.

By the end of the decade, Technion had expanded to include the Technion Research and Development Foundation, the Graduate School, and faculties in Agricultural Engineering, Chemistry and Industrial Engineering and Management.

1960s – Turning International and Interdisciplinary

During the 1960s, the Technion opened its doors to hundreds of students from the developing countries of Africa and Asia. Scores of Technion faculty members provided technological assistance to various countries worldwide, often under the auspices of United Nations agencies.

Recognizing the growing trend in interdisciplinary activity, Technion established several new departments, including Biomedical Engineering, Computer Science, Applied Mathematics, and the Solid State Institute.

In 1969, Technion established the Faculty of Medicine, one of the few medical schools worldwide to be affiliated with an institute of technology.

1970s – Turbulent Times

The 1970s in Israel were marked by extremes – from the trauma and tragedy of the Yom Kippur War to the optimism and hope of Israel's peace agreement with Egypt. Throughout the upheaval and change, Technion remained at the forefront of the nation's activities – from producing technologies for guaranteeing Israel's future security, to planning...
cooperative regional research projects in subjects such as desalination and nuclear energy. The establishment of the Samuel Neaman Institute for Advanced Studies in Science and Technology at the Technion in 1978 further encouraged the interaction of academia, industry and government.

1980s – The Rise of High-Tech

In the 1980s, Technion-based research paved the way for the rapid expansion of Israel’s high-tech industries. From the birth of fiber-optics and the development of optoelectronics, Technion graduates were, and continue to be, at the forefront of technological innovations.

In the 1980s, Technion's world-wide reputation for excellence was strengthened through intensified research in various fields spanning from nuclear power options for Israel to a new program in marine engineering, and pioneer work in the field of industrial robotics.

1990s – Reaching for the Stars

In the early '90s, massive immigration from the former Soviet Union boosted the student population from 9,000 to 10,500.

Multidisciplinary centers of excellence were established, ties with industry were strengthened, new academic programs were developed, and a massive campus expansion program was launched, including construction of The Henry and Marilyn Taub and Family Science and Technology Center, which houses the western world's largest computer science faculty.

In 1998, Technion successfully launched the "Gurwin TechSat II" microsatellite, making Technion one of five universities with a student program that designs, builds, and launches its own satellite.
**2000 and beyond – No Stopping at the Top**

As Israel strives to maintain its economic independence, it recognizes, as do other nations, that a strong economy depends closely upon the education of its citizens. The Technion and its graduates have risen to this challenge, providing the creative edge and the know-how to build the economy.

Technion graduates comprise the majority of Israeli-educated scientists and engineers, and constitute over 70% of the country’s high-tech industry's founders and managers. These sectors are growing at phenomenal rates, and are driving the country's burgeoning exports. They will clearly continue to play a key role in shaping the country's economic independence.

In the twenty-first century, Technion graduates will reach new heights as they search to meet the towering challenges of the new millennium. From environmental issues, biotechnology and genetics to the frontiers of cyberspace and outer space, Technion researchers are committed to securing a bright and prosperous future.
Present Day Technion

From the Technion official website

2010 Student Population

Undergraduate Studies: 9,401  
Master's Degrees: 2,301  
Doctoral Degrees: 963  
TOTAL: 12,665

Degrees Awarded (from 1927-2010 inclusive): 90,604  
Faculty Members: 536  
Clinicians, Adjuncts, & Instructors: 994

Campus

Technion City: 1,325,000 square meters (14,262,181 square feet or 0.5 square miles)  
Buildings: 87  
Student Dormitory Beds: 4,021  
Faculties: 18

From the Lab to the Marketplace

Technion graduates comprise the majority of Israeli-educated scientists and engineers, constituting over 70% of the country's founders and managers of high-tech industries. Due to the ingenuity of Technion alumni, Israel is now home to the greatest concentration of high-tech start up companies anywhere outside of the Silicon Valley. 80% of Israeli NASDAQ companies are led by Technion graduates. High-tech industry now accounts for more than 54% of Israel's industrial exports, and over 26% of the country's exports. 135 out of every 10,000 workers in Israel are scientists and engineers, compared to the USA, in second place with 85 out of every 10,000 workers. Nine out of every 1,000 workers are engaged in Research and Development (R&D), nearly double the rate of the USA and Japan. 74% of managers in Israel's electronic industries hold Technion degrees.
The Janet and David Polak Cancer and Vascular Biology Research Center

From the David & Janet Polak Cancer and Vascular Biology Research Center official website

The Janet and David Polak Cancer and Vascular Biology Research Center, The Rappaport Faculty of Medicine Research Institute and Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

The center was established in 2003 to promote an in-depth interdisciplinary basic and clinical research on the control of cellular and molecular processes that are involved in cancer initiation and progression. We strongly believe that the understanding of basic biological processes that underlie normal development and their deregulation in cancer, is crucial for our ability to identify molecular targets for early detection, intervention, and cure of the disease. We are interested in a broad view of cancer - from the single malignantly transformed cell and its microenvironment, through the entire tumor in the animal. We focus on targeted ubiquitin-mediated degradation of key regulatory proteins that are involved in malignant transformation [Prof. Aaron Ciechanover (Nobel Prize in Chemistry 2004)], angiogenesis and cancer progression (Prof. Gera Neufeld), metastasis and tumor microenvironment (Prof. Israel Vlodavsky), as well as genetic and genomic dissection of embryonic and cancer transcriptional networks (Dr. Amir Orian). Towards these objectives, we combine molecular, biochemical, cell biological with Drosophila genetic and genomics experimental approaches, as well as employing advanced models of angiogenesis and metastasis.

We believe that scientific excellence and collegiality go together. Therefore, the center has an open and friendly atmosphere, creating a highly stimulating environment. It currently trains 45 graduate students, post-doctoral fellows, clinicians and researchers that are at the heart of our research. Formal and informal collaborations between individuals and laboratories are on-going and encouraged. We are running a series of joint seminars to which we invite researchers from Israel and abroad. The Center has advanced state-of-the-art microscopic and image analysis equipment, as well as other shared pieces of infrastructural equipment. The center is an integral part of the Faculty of Medicine and the Rappaport Research Institute which are home for excellent research groups, and enjoys their advanced Interdepartmental Equipment Unit. It is also adjacent to the Rambam Medical Center - the major hospital in the north of Israel - which provides us with access to rich clinical material and collaboration with clinicians. Many of them spend active research periods in our laboratories and bring the bench closer to the patient bed and vice versa. The Center is in an active phase of growth, and offers excellent research opportunities, space and facilities for students, post-doctoral fellows, and physicians.
Research Interest: Protein Turnover

By Dr. Aaron Ciechanover
From the David & Janet Polak Cancer and Vascular Biology Research Center official website

Intracellular protein degradation and mechanisms of cancer

One main focus of research in our laboratory is the involvement of the ubiquitin proteasome system (UPS) in differentiation and the pathogenesis of malignant transformation. To deconvolute the process which is enormously complex and involves numerous distinct mechanisms, we decided to study two different, yet related processes: (i) activation of the NF-κB transcriptional regulator, and (ii) evasion of apoptosis.

(i) The transcriptional activator NF-κB has a strong anti-apoptotic activity. It promotes cell division, migration, motility angiogenesis, and adhesion, and it mediates the inflammatory response. Not surprisingly, it is constitutively up-regulated in many malignancies. It is activated via a two step ubiquitin-mediated mechanism: (a) processing of the precursor proteins p105 and p100 to the active subunits, p50 and p52, respectively, and (b) signal-induced degradation of the inhibitor IκBα that sequesters NF-κB inactive in the cytosol. Signal-induced degradation of the inhibitor results in translocation of the active factor to the nucleus where it initiates specific transcription. We are particularly interested in the mechanism(s) that lead to processing of the precursor proteins. These events are exceptional, as in most cases the ubiquitin system destroys its target substrates completely, while here it processes them in a limited manner to release short, active subunits from longer inactive precursors. We aim to identify the characteristics of the p105 and p100 molecules that render them resistant to degradation but sensitive to processing, and to purify and characterize the ubiquitin ligases, E3s, involved. We hypothesize that the ligases are up-regulated in different malignancies, contributing to the high level of NF-κB in these tumors.

(ii) Evasion of apoptosis or gradual development of resistance to genotoxic stimuli such as irradiation or chemotherapeutic agents, is a hallmark of malignant cells as their behavior becomes more aggressive. We are studying the regulation of Inhibitors of Apoptosis Proteins, many of them are RING finger ubiquitin ligases, E3s, that inhibit apoptosis by targeting caspases for ubiquitination and subsequent degradation. A feature characteristic to many RING finger E3s is their ability to catalyze auto-ubiquitination and target themselves for degradation. Thus, their activity is balanced between self destruction and destruction of their substrates. The activity of IAPs must be tightly regulated, as their untoward activation will inhibit apoptosis, while decreased activity will induce it. A group of recently discovered pro-apoptotic proteins, cytosolic Reaper, Grim and Hid in Drosophila, and mitochondrial Smac/Diablo and Omi/Htr2A in mammalian cells, act to down regulate them, probably by stimulating their auto-ubiquitination and targeting them for degradation. In contrast, NF-κB for example, acts to increase IAPs expression...Our aim is to better understand the regulation of IAPs, so it will be possible to down-regulate them and re-sensitize malignant cells to apoptosis-inducing agents.
**Non-canonical ubiquitination, and regulation of transcription and of elements of the ubiquitin system**

An additional major focus of interest in our laboratory involves “non-canonical” modes of ubiquitination. We identified a novel mode of ubiquitination in which modification occurs at the N-terminal residue of the substrate rather than on internal lysine residues. This modification is essential for the degradation of naturally occurring lysine-less proteins, such as the cell cycle regulator p16$^{\text{INK4a}}$, that cannot be modified otherwise. We have also shown that the auto-ubiquitinating activity of Ring1B, a ubiquitin ligase..., does not serve to target the protein for degradation, but rather to activate its ligase activity towards histone H2A. Accordingly, the chains generated are not the “canonical” lysine48-based chains recognized by the 26S proteasome for degradation, but rather lysine6, 27-based mixed and most probably doubly branched chains that activate the ligase by recruiting to the complex additional, yet to be identified proteins. The finding that the auto-ubiquitinating activity of the Ring1B ligase does not lead to its degradation, implies the ligase itself must be degraded following targeting by an exogenous ligase. Not only that we are searching for this ligase, but this finding opened a whole new line of research in the laboratory - how the components of the ubiquitin system are regulated – or how the controllers are being controlled.
**Recent Lectures by Dr. Ciechanover**

“Life and death – Why our proteins have to die so we shall live”

April 3, 2008

Lecture given as part of the 1st Association of Southeast Asian Nations (ASEAN) event series “Bridges – Dialogues Towards a Culture of Peace,” facilitated by the International Peace Foundation

Abstract: Between the 1950s and 1980s, most studies in biomedicine focused on the central dogma - the translation of the information coded by DNA to RNA and proteins. Protein degradation was a neglected area, considered to be a non-specific, dead-end process. While it was known that proteins do turn over, the high specificity of the process - where distinct proteins are degraded only at certain time points, or when they are not needed any more, or following denaturation/misfolding when their normal and active counterparts are spared - was not appreciated. The discovery of the lysosome by Christian de Duve did not significantly change this view, as it was clear that this organelle is involved mostly in the degradation of extracellular proteins, and their proteases cannot be substrate-specific. The discovery of the complex cascade of the ubiquitin solved the enigma. It is clear now that degradation of cellular proteins is a highly complex, temporally controlled, and tightly regulated process that plays major roles in a variety of basic cellular processes such as cell cycle and differentiation, communication of the cell with the extracellular environment and maintenance of the cellular quality control. With the multitude of substrates targeted and the myriad processes involved, it is not surprising that aberrations in the pathway have been implicated in the pathogenesis of many diseases, certain malignancies and neurodegeneration among them, and that the system has become a major platform for drug targeting.

To read a transcript of the full lecture, visit [http://peace-foundation.net.7host.com/keynote_speeches.asp](http://peace-foundation.net.7host.com/keynote_speeches.asp)

“Science and Technology as a Novel Language of Peace”

October 30, 2009

Lecture given as part of the 3rd Association of Southeast Asian Nations (ASEAN) event series “Bridges – Dialogues Towards a Culture of Peace,” facilitated by the International Peace Foundation

Abstract: This lecture is divided into two parts. In the first part, Dr. Ciechanover provides a brief introduction about himself, expounding living in a small country, developing a career there and eventually making it to the international platform. He also discusses career choices and provides advice about how to make decisions when approaching crossroads. In the
second part, Dr. Ciechanover discusses the challenges that lay ahead with respect to medicine, as well as some bioethical highlights and bioethical problems that not only the biomedical community is facing, but that everyone is facing.

To read a transcript of the full lecture, visit http://peace-foundation.net.7host.com/keynote_speeches.asp

“Drug Development in the 21st century: Are we going to cure all diseases?”

November 10-11, 2010

Lecture to be given at Purdue University as part of the Honeywell-Nobel Initiative

Abstract: Many important drugs such as penicillin, aspirin, or digitalis, were discovered by serendipity - some by curious researchers who noted an accidental phenomenon, some by isolation of active ingredients from plants known for centuries to have a specific therapeutic effect. Other major drugs like statins were discovered using more advanced technologies, such as targeted screening, yet, the discoverers were looking for a different effect. In all these cases, the mechanisms of action of the drug were largely unknown at the time of their discovery, and were discovered only later. With the realization that not all patients with diseases that physically and histopathologically appear to be the same - different malignancies for example - respond similarly to treatment, and their clinical behavior is different, we have begun to understand that their molecular basis is distinct. Accordingly, we are exiting the era where our approach to treatment is “one size fits all”, and enter a new one of “personalized medicine” where we shall tailor the treatment according to the patient’s molecular/mutational profile. Here, unlike the previous era, the understanding of the mechanism will drive the development of the new drugs. This era will be characterized by the development of technologies where sequencing and processing of individual genomes will be cheap (US$ <1,000) and fast (a few minutes), by identification and characterization of new disease-specific molecular markers and drug targets, and by design of novel, mechanism-based, drugs to modulate the activities of these targets. It will require a change in our approach to scientific research and development and to education, where interdisciplinarity will dominate and replace in many ways the traditional, discipline-oriented approach.

A brief overview of this lecture can be found at http://2010smtpphysics.wikispaces.com/Public+Lecture+on+Drug+Dev+in+21st+Century,+LKY+Distinguished+Visitor+Program
Current Work at the Technion

Chapter Study Questions

1. Perform your own research on the Technion. If you were to attend, what would you study? What interests you most?

2. How does Dr. Ciechanover’s current research at the Technion relate to his previous scientific work?

3. How does Dr. Ciechanover’s involvement with the Technion relate to his commitment to education? Does the Technion defy Dr. Ciechanover’s statements about the woes of the Israeli education system in any way? If so, how?

4. Choose one of Dr. Ciechanover’s recent lectures to read in full. Which one did you choose and why? What did you learn? What questions does this lecture raise for you?
VI. Reference Materials

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Publications by Dr. Ciechanover: 2004-Present


## Additional Resources

### Publications


Kresge, Nicole, Robert Simoni, and Robert Hill. "The Discovery of Ubiquitin-mediated Proteolysis by Aaron Ciechanover, Avram Hershko, and Irwin Rose." *Journal of Biological Chemistry* (2006): 281: e32. [http://www.jbc.org/content/281/40/e32.full#ref-list-1](http://www.jbc.org/content/281/40/e32.full#ref-list-1)


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC154126/


http://bentham.org/lddd/sample/lddd2-1/014AJ.pdf

**Online Resources**

**Alzheimer’s Association**
www.alz.org

**Alzheimer Research Forum**
www.alzforum.org

**Cystic Fibrosis Foundation**
www.cff.org

**Honeywell Nobel Interactive Studio**
www.honeywellscience.com

**International Peace Foundation**
peace-foundation.net

**Israel Defense Forces**
dover.idf.il/IDF/English

**Israel Government Portal**
www.gov.il/firstgov/english

**Jewish Virtual Library**
www.jewishvirtuallibrary.org

**Lorry I. Lokey Interdisciplinary Center for Life Sciences and Engineering**
lokey.technion.ac.il

**My Jewish Learning**
www.myjewishlearning.com
National Parkinson Foundation
www.parkinson.org

Nobel Laureate Meetings at Lindau
www.lindau-nobel.org

Parkinson Research Foundation
www.parkinsonresearchfoundation.org

Technion-Israel Institute of Technology
www1.technion.ac.il/en

The David and Janet Polak Cancer and Vascular Biology Research Center
www.technioncancer.co.il

The Official Web Site of the Nobel Prize
nobelprize.org

The Royal Swedish Academy of Sciences
www.kva.se/en

Vega Science Trust
vega.org.uk

Videos

Aaron Ciechanover Discusses Nobel Prize-Winning work with Protein
• Aaron Ciechanover discusses his Nobel Prize-winning work on protein destruction and how this knowledge impacts drugs in development. http://www.columbia.edu/cu/news/media/05/356_Ubiquitin_Proteolytic_System/index.html

Aaron Ciechanover in Interview: Selectivity and Specificity in a Destructive Process

Breaking down Alzheimer’s with Aaron Ciechanover
• Alzheimer's disease is caused by abnormal clumps or aggregations of proteins in the brain. Simon Pöpsel is about to embark on PhD work on a protein that might help us to treat this devastating disease, and Nobel Prize winning biochemist Aaron Ciechanover is clearly excited by his ideas. http://www.nature.com/video/lindau2009/index.html
Cracking the Code of Life

- The companion website to *Cracking the Code of Life*, a two-hour special, hosted by ABC "Nightline" correspondent Robert Krulwich, which chronicles the race to capture one of the biggest prizes in scientific history: the complete letter-by-letter sequence of genetic information that defines human life - the human genome. Includes additional resources and teacher’s guide.
  http://www.pbs.org/wgbh/nova/genome/

Drug Development in the 21st Century – Are We Going to Cure All Diseases and at What Cost?

- Is it possible that drugs will be developed to cure all diseases? Dr. Ciechanover shares some thoughts on whether personalized medicine is going to be the solution to curing all diseases, where personalized medicine is coming from, and where it is going to take us.

Finding Cures is Hard

- This video segment from NOVA: "Cracking the Code of Life" explores the difficulty of finding cures for genetic diseases like cystic fibrosis, even after the genetic defects that caused the disorders have been identified.
  http://www.pbs.org/teachers/connect/resources/5272/preview/

Nobel Highlights

- A look at the lives and work of the 2004 Nobel Laureates in Chemistry.

Nobel Lecture by Dr. Aaron Ciechanover

- Intracellular Protein Degradation: From a Vague Idea thru the Lysosome and the Ubiquitin-Proteasome System and onto Human Diseases and Drug Targeting

Nobel Lecture by Dr. Avram Hershko

- The Ubiquitin System for Protein Degradation and some of its Roles in the Control of the Cell Division Cycle

Nobel Lecture by Dr. Irwin Rose

- Ubiquitin at Fox Chase

The 2009 Lindau Nobel Laureate Meeting: Aaron Ciechanover, Chemistry 2004

- An interview with Aaron Ciechanover at the 2009 Lindau Nobel Laureate Meeting in Lindau, Germany.
  http://www.jove.com/index/details.stp?ID=1559

The Vega Science Trust

- A video interview with Dr. Ciechanover recorded in 2006 by the Vega Science Trust
  http://vega.org.uk/video/programme/287
Resources for Educators

Teacher’s Domain
- Digital media for the classroom and professional development
  http://www.pbs.org/teachers/connect/resources/5272/preview/

Interviews with Australian Scientists: Dr. Rohan Baker
- Provides an extract of an interview with Dr. Baker, in which he describes what ubiquitin is and why he finds researching it so interesting, as well as focus questions and activities for students.

Ubiquitination: The Proteasome and Human Disease
- MIT Open Courseware (undergraduate level) featuring readings, lecture notes, and assignments.
The Aaron Ciechanover Project: Living Science

presented by

The Echo Foundation

ART & PHOTOGRAPHY CONTEST

GUIDELINES

The debate between religion and science has been ongoing for centuries, and perhaps even millennia. At times, Dr. Ciechanover has offered unique views about religion versus science. Create a piece of artwork that conveys your beliefs about the compatibility or incompatibility of religion and science.

**WHAT:** Presented by The Echo Foundation, *The Aaron Ciechanover Project: Living Science* offers art contests in two categories: **ART AND PHOTOGRAPHY**. Students are invited to respond to the above challenge in either medium.

**WHO:** The contest is open to all Charlotte-area high school students, grades 9 – 12.

**WHEN:** Entry forms and submissions must be postmarked or received by The Echo Foundation at 1125 East Morehead Street, Suite 106, Charlotte, NC 28204, by **Monday, March 7, 2011**.

**HOW:** Entry forms may be downloaded from The Echo Foundation website at [http://www.echofoundation.org](http://www.echofoundation.org) or obtained at The Echo Foundation office. No student name should appear on the front of a submission and an entry form must accompany each entry.

**PURCHASE AWARDS AND CATEGORIES:** First ($100), second ($75) and third ($50) place prizes will be given in each of the two categories: art and photography. All other art and photography entries can be reclaimed following the contest’s judging.

**JUDGING AND RULES:** Educators and professionals in the corresponding fields will serve on the judging panel. The panels reserve the right to not award a cash prize in a category if the submissions do not meet the qualifications for entry. 2-D original artwork and photography may not exceed 36” in height or width.

For more information contact The Echo Foundation at 704-347-3844 or email questions to EchoJustice@aol.com.
ART & PHOTOGRAPHY CONTEST: 
OFFICIAL ENTRY FORM

This completed and signed form must accompany each entry. Copies of this form are permissible.
Two-dimensional original works of art no larger than 36” x 36” will be accepted.

Please Print or Type:

Full Name: _______________________________         Male  Female
Address: ________________________________________________________________
City: _______________________________ State: __________ Zip: ___________________
Phone: ________________ Email: ___________________ School: ______________________
Current Class Status:  □ Freshman  □ Sophomore  □ Junior  □ Senior

Title of entry and brief description:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

I give permission for my student’s art entry to be used in future publications and/or exhibits.

Parent/Guardian Signature                       Date

Entry form and submission must be postmarked or received by
The Echo Foundation, 1125 East Morehead Street, Suite 106,
Charlotte, NC 28204, by Monday, March 7, 2011.

For more information contact The Echo Foundation at 704-347-3844 or
email questions to EchoJustice@aol.com.
The debate between religion and science has been ongoing for centuries, and perhaps even millennia. At times, Dr. Ciechanover has offered unique views about religion versus science. Within your personal framework of beliefs, are science and religion compatible? How do you reconcile the two? How can religion inform science for the benefit of humanity and vice versa? Providing precise examples, create an essay or poem that explains your point of view.

**WHAT:** Presented by The Echo Foundation, *The Aaron Ciechanover Project: Living Science* offers writing contests in two categories: ESSAY AND POETRY. Students are invited to respond to the above challenge in either medium.

**WHO:** The contest is open to all Charlotte-area high school students, grades 9 – 12.

**WHEN:** Entry forms and submissions must be postmarked or received by The Echo Foundation at 1125 East Morehead Street, Suite 106, Charlotte, NC 28204, by **Monday March 7, 2011**.

**HOW:** Entry forms may be downloaded at [http://www.echofoundation.org](http://www.echofoundation.org), The Echo Foundation website, or obtained at The Echo Foundation office. No student name should appear on the front of a submission and an entry form must accompany each entry.

**PURCHASE AWARDS AND CATEGORIES:** First ($100), second ($75) and third ($50) place prizes will be given in both categories: essay and poetry.

**JUDGING AND RULES:** Educators and professionals in the corresponding fields will serve on the judging panel. The panels reserve the right to not award a cash prize in a category if the submissions do not meet the qualifications for entry. All written entries must be typed (double-spaced). Word limit for essays is 1,500; poetry has no limit on length.

For more information contact The Echo Foundation at 704-347-3844 or email questions to EchoJustice@aol.com.
The Aaron Ciechanover Project:  
Living Science  
presented by  
The Echo Foundation  

ESSAY & POETRY CONTEST:  
OFFICIAL ENTRY FORM  

******  
This completed and signed form must accompany each entry. Copies of this form are permissible. 
Essays may be no more than 1,500 words, must be printed in size 12 font and double-spaced.  

Please Print or Type:  
Full Name: ____________________________________________  □ Male  □ Female  
Address: ____________________________________________________________________  
City: __________________________ State: __________ Zip: ___________________  
Phone: ______________ Email: ___________________ School: ____________________  
Current Class Status:  □ Freshman  □ Sophomore  □ Junior  □ Senior  

Title of entry and brief description:  
_____________________________________________________________________________  
_____________________________________________________________________________  

I give permission for my student’s essay/poetry entry to be used in future publications and/or exhibits.  

__________________________________                        _____________________________  
Parent/Guardian Signature                     Date  

Entry form and submission must be postmarked or received by  
The Echo Foundation, 1125 East Morehead Street, Suite 106,  
Charlotte, NC 28204, by Monday, March 7, 2011.  

For more information contact The Echo Foundation at 704-347-3844 or  
email questions to EchoJustice@aol.com.  

The Echo Foundation 133  The Aaron Ciechanover Project
AN INTRODUCTION

The Echo Foundation promotes justice and inspires hope through education, creative acts of service, and the development of leadership for a more humane world.

Through comprehensive educational programs, The Echo Foundation equips individuals with moral and intellectual tools necessary to create positive change in their local and global communities. Echo initiatives use the power of example to educate about critical issues of human rights and social justice. Experiential learning opportunities, programs using the arts in service to humankind, and facilitated dialogue in the pursuit of innovative solutions are hallmarks of the organization.

The foundation was created in 1997 by Stephanie Ansaldo, with Nobel Laureate Elie Wiesel serving as Honorary Chair, following Wiesel’s visit to Charlotte that year. As the community-wide project Against Indifference concluded, Wiesel challenged the community to act on its convictions of human dignity, justice, and moral courage. He also offered his assistance in developing programs to address critical issues facing humanity.

Today Echo delivers programming through five core initiatives. The foundation has hosted 19 humanitarians, Nobel Laureates, and world leaders, served over 600,000 students, and forged partnerships worldwide. Recent projects have focused on Dr. Paul Farmer & Partners In Health; Africa expert and activist, John Prendergast; Rwandan Bishop John Rucyahana; Science Nobel Laureates, Günter Blobel, Edmond Fischer, Christiane Nüsslein-Volhard, Douglas Osheroff, and Robert Richardson; founder of Doctors without Borders, Bernard Kouchner; Earth Institute Director, Jeffrey Sachs; and others. For more information about The Echo Foundation, visit www.echofoundation.org.
THE ECHO FOUNDATION

FIVE INITIATIVES

The Echo Foundation Mission: “to promote justice and inspire hope through education, creative acts of service, and the development of leadership for a more humane world.” Echo promotes its mission through the implementation of Five Initiatives.

- **Voices Against Indifference**: Through bringing renowned humanitarians to Charlotte as a catalyst for education, and with diversity of race, class and culture as our primary focus, The Echo Foundation creates educational programs centered on the message of our annual guest. *Voices Against Indifference* builds bridges across racial divides by bringing students from all corners of Charlotte-Mecklenburg together to learn about the messages of our guests. In other words, thinking globally and acting locally – taking lessons learned around the world and seeking to apply the solutions locally. An extension to this initiative is Echo’s Annual Award Dinner at which the International Humanitarian is the Keynote Speaker and a local hero is chosen to receive the Echo Award Against Indifference.

- **Forum for Hope**: Believing that the tone and culture of an organization begins at the top, Echo invites 20 leaders from the Charlotte community to travel together for the purpose of exposure to individuals who have, from a humanitarian perspective, shaped the world in a positive way. Our inaugural journey was to Boston for a round table discussion with Echo Foundation Honorary Chair, Elie Wiesel. Participants met twice prior to traveling to build unity around the mission of the initiative and to establish goals and measures for success. A steering committee was formed to identify participants ensuring representation from professional, educational, religious, medical and arts communities with an emphasis on race, ethnicity and gender diversity.

- **Living Together in the 21st Century**: *Living Together in the 21st Century* is an education outreach project for 2nd grade students originated by Nobel Peace Laureate, Elie Wiesel, with involvement by child activist, Jonathan Kozol, and created by Charlotte-Mecklenburg teachers. LT is a broad-based curriculum that focuses on living together in harmony and teaches problem solving strategies, conflict resolution and respect for others. The underlying mission of the project is to simultaneously begin to build compassion for people of all races, cultures and backgrounds, and to teach life skills in young children that will prepare them to live in our society non-violently. The curriculum is mandatory in all Charlotte-Mecklenburg elementary schools.

- **Footsteps Global Initiative**: Our belief is that travel and hands-on experiences have the capacity to transform students in a way that transcends classroom learning; only by “doing” can young people fully appreciate the challenges that face them as future leaders. This leadership initiative for regional high school students promotes awareness and global citizenship through international travel and service. Competitively selected Ambassadors of the initiative participate in yearlong programming that combines intensive study, volunteerism and travel to locations of great humanitarian interest.

- **Books Beyond Borders**: Encourages international understanding and action on behalf of others by helping Charlotte students furnish libraries for children around the world.
THE ECHO FOUNDATION

- International Board of Advisors -

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Nobel Laureate for Peace, 1986

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Henry Louis Gates, Jr., Chair, Department of African & African American Studies, Harvard University
Kerry Kennedy, International Human Rights Activist and Author
Dr. Bernard Kouchner, Founder, Doctors Without Borders
Jonathan Kozol, Child Advocate
Jeffrey D. Sachs, Director, The Earth Institute, Columbia University
Harry Wu, Executive Director, The Laogai Research Foundation

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Sally Robinson, Community Volunteer
F. William Vandiver, Retired Executive, Bank of America
The Honorable Melvin Watt, United States Congressman, North Carolina
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