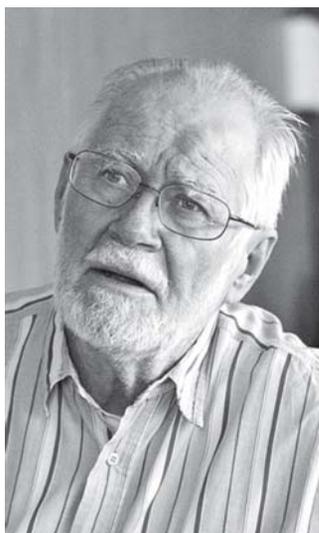


NOBEL PRIZES IN SCIENCE : 2017

CHEMISTRY

The Royal Swedish Academy of Sciences announced on October 4, 2017 the award of the Nobel Prize in Chemistry 2017 to Jacques Dubochet (University of



Jacques Dubochet

Jacques Dubochet, born in 1942 in Aigle, Switzerland, received Ph.D. degree in 1973 from the University of Geneva and University of Basel, Switzerland. He is now an Honorary Professor of Biophysics at the University of Lausanne, Switzerland. **Joachim Frank**, born in 1940 in Siegen, Germany had his Ph.D. in 1970 from the Technical University of Munich, Germany. He is currently a Professor of Biochemistry and Molecular Biophysics and of Biological Sciences at the Columbia University, New York, USA. **Richard Henderson**, born in 1945 in Edinburgh, Scotland earned his Ph.D. degree in 1969 from the Cambridge University, UK. At present he is the Programme Leader, MRC Laboratory of Molecular Biology, Cambridge, U.K.

Indeed, hundreds of biomolecules have now been imaged using cryo-electron microscopy (cryo-EM). As a result, numerous astonishing complex machineries of life have been unveiled in atomic resolution. Some of the glaring examples are molecular complexes governing circadian rhythms, proteins conferring resistance to

chemotherapy and antibiotics, complex light-capturing reactions involved in photosynthesis, a kind of pressure sensor that enables us to hear and Salmonella's injection needle for attacking cells. The very recent generation of 3D image of the Zika virus deserves a special mention.

Until mid-1900s it was known that the fundamental biomolecules, viz. proteins, DNA and RNA play crucial roles in cells. But there was no knowledge as to how these molecules looked like. In the 1950s, the discovery of X-ray crystallography first

brought to fore the image of these molecules in the solid state. But it was not enough since biomolecules display their bioactivity by their dynamics in solution. The situation was improved by the discovery of NMR in the early 1980s. But solution-phase NMR work well only for comparatively small proteins, and many biomolecules even failed to crystallise. Hence, Henderson abandoned X-ray crystallography in the 1970s and was on the lookout for a solution. Conceivably, here lies the root to the story of Nobel Prize 2017 in Chemistry.



Richard Henderson



Joachim Frank

For his work with membrane proteins, Henderson resorted to transmission electron microscopy (TEM). But this too was not useful

since TEM requires vacuum, whereby water evaporates, the proteins dry out, collapse and lose their natural structures, thus rendering the resulting images useless. Henderson then turned to bacteriorhodopsin, a membrane-bound protein involved in natural photosynthesis. He placed the protein under TEM and took pictures from many different angles. In 1975, an unrefined 3D model of the protein thus emerged with a resolution of 7 Å, the best of its kind till then. But his aim was to achieve a resolution of 3 Å. Over the years, cryotechnology developed, in which samples were cooled in liquid nitrogen during TEM, thus protecting the biomolecules from being damaged by the incident electrons. Using cryotechnology and EM, Henderson was finally able to generate in 1990 the first 3D structure of bacteriorhodopsin in atomic resolution.

Joachim Frank in New York was after the same objective but from a different angle. In 1975, he tried to develop a computer-mediated theoretical strategy, a mathematical model, to merge 2D images of proteins, derived from TEM, into a 3D-structure. He could complete the algorithms for the software in 1981. In mid-1980s, he used his approach to generate the 3D model of the surface of ribosome, a huge molecular machinery that builds up proteins inside the cells. Frank's image processing was crucial to the development of cryo-EM.

Around 1978, Jacques Dubochet came to Heidelberg to solve the basic problem of an electron microscope, viz. how to vaporise water without getting the biomolecules damaged when exposed to vacuum. He visualised that if water could be rapidly cooled to form a glass, known as vitrified water, instead of ice crystals, electron beam would diffract evenly and form a uniform background. In 1982, he made a breakthrough – he vitrified water by cooling the biomolecules in aqueous environment in liquid ethane (ca. 190°) which, in turn, was cooled in liquid nitrogen. He developed a technique which forms the basis of current cryo-EM. He dissolved various viruses in water, spread the solution across a fine metal mesh as a thin film, shot (using a bow-like construction) the net into liquid ethane when water vitrified. In 1984, Dubochet published the 3D images of viruses of different shapes and sizes in an ambience of vitrified water.

The development of modern cryo-EM thus began. In 1991, Frank used Dubochet's water vitrification method to prepare, using his own software, a 3D image of ribosomes with a resolution of 40 Å. Since the images looked like blobs, cryo-EM at this stage was also called 'blobology'. The technical hurdle of improving resolution was finally overcome in 2013, when a new type of electron detector came into use.

Frank told journalists gathered at the Royal Swedish Academy of Sciences in Stockholm that "*cryo-electron microscopy is about to completely transform structural biology.*" Venki Ramakrishnan, the recipient of Nobel Prize in Chemistry in 2009, voiced similarly: "*It has totally revolutionised structural biology.*"

When interviewed over telephone by the Chief Scientific Officer of Nobel Media, the three Nobel Laureates responded as follows.

Jacques Dubochet: "*If you have them in ice, or if you have them without water, the molecules, like fish, are dead.*" **Joachim Frank** (when he was asked if he woke up in the morning by the phone call from the Royal Swedish Academy): "*Yeah, —, we have a new dog and she wakes up very early in the morning. So this time it was the Nobel prize! [Laughs] Normally it's the dog that wakes us up.*" **Richard Henderson:** "*It's opened up a previously unapproachable area of structural biology.*"

Curiously, Frank referred to a photograph of his new dog Daisy taken by him in Central Park in the weekend just preceding October 4. This photo reflects Frank's work in cryo-EM, in which multiple 2D images are transformed into high resolution 3D structures. In his own version: "*I was intrigued by the geometric arrangement, and the way 3D object (Daisy), the camera man (me), and their shadows are all depicted at the same time.*" In Adam Smith's words, it was "*The whole Nobel Prize in one picture.*"



Photo of Daisy taken by Frank

The ground-breaking discovery of cryo-EM by the trio have "*moved biochemistry into a new era*", said the Royal Swedish Academy of Sciences. Their work has brought "*the greatest benefit to mankind.*" Each corner of the cell can now be imaged in atomic detail, and "*biochemistry is all set for an exciting future.*" □

Professor Manas Chakrabarty, FRSC
Formerly, Department of Chemistry
Bose Institute, Kolkata

PHYSICS

The Noble Prize in Physics for the year 2017 has been awarded, one half to Rainer Weiss, and the other half jointly to Barry C. Barish and Kip S. Thorne “for decisive contributions to the LIGO detector and the observation of gravitational waves”¹.

The General Theory of Relativity predicts the existence of gravitational waves from rotating massive objects (e.g. black hole binaries, or a pair of neutron stars revolving about each other). The gravitational wave front pair may be envisioned to spiral out from the rotating mass pair at the velocity of light.



A pictorial representation of a gravitational wave²

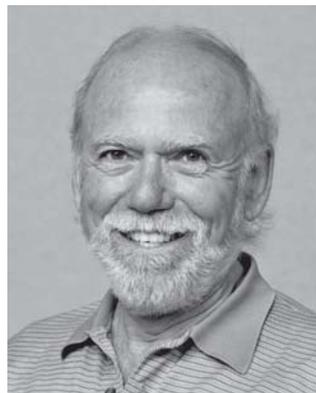
The passage of the gravitational wave is related to a change in space-time metric. The change in the space-time metric can be detected by Laser Interferometer Gravitational-Wave Observatories^{2,3} (LIGO) which is a multinational collaboration. Two such observatories are situated in USA; one at Livingston, Louisiana and the other at Hanford near Richland, Washington, and are separated by about 3000 km. The LIGO is similar to the Michelson’s interferometer, except that it has two long Fabry-Perot cavities, in two orthogonal directions, where the interference of two coherent beams at the beam splitter forms fringes. The change in the length of any arm (or a length of any one of the cavities) would result in change in the fringe. Here the two arms of the LIGO are comprised of two evacuated tubes 4 km long.



Rainer Weiss

The passage of the gravitational wave is expected elongate (or shorten) one of the arms with respect to the other, thereby disturbing the fringe. The similarity with the Michelson interferometer ends there, as the LIGO is enormously sensitive and can detect a

length variation of about an attometer⁴ (1 attometer = 10^{-18} m) and uses homodyne detection and frequency dependent squeezed light states to improve the signal to noise ratio. Simultaneous observation of the gravitational wave signal GW150914 at the two observatories proved the existence of the gravitational wave. LIGO collaboration in India (INDIGO) has also been planned.



Barry Clark Barish

Technology and an adjunct professor at Louisiana State University. He invented the laser interferometric technique which is the basis for operation of LIGO.

Barry Clark Barish (b 1936, Omaha USA) is a Linde Professor of Physics, Emeritus at California Institute of Technology. He is a leading expert on gravitational waves.



Kip Stephen Thorne

Kip Stephen Thorne (b 1940, Logan, USA) was the Feynman Professor of Theoretical Physics at the California Institute of Technology and is known for his contributions in gravitational physics and astrophysics. □

Source

1. Nobelprize.org
2. Wikipedia (LIGO, Gravitational Wave, Gravitational-Wave Observatory)
3. The LIGO Scientific Collaboration, *Nat. Phys.* **7**, 962-965 (2011)
4. S.E. Whitcomb, *Proc. Internat. Symp. Modern Problems in Laser Physics*, August 27-September 3, (1995); Novosibirsk, LIGO Publication P950007-01-R
5. Photo credits: https://en.wikipedia.org/wiki/File:Rainer_Weiss_-_December_2006.jpg, <https://en.wikipedia.org/wiki/File:05-0367-92D.hr.jpg>, https://en.wikipedia.org/wiki/File:Kip_Thorne_at_Caltech.jpg

B.K. Chatterjee
Department of Physics,
Bose Institute, Kolkata 700009

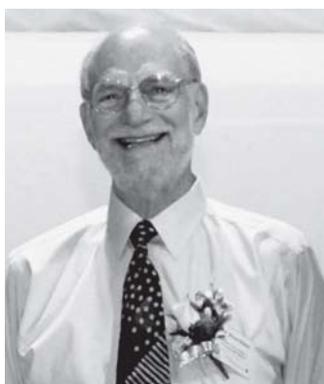
PHYSIOLOGY OR MEDICINE

Nobel Prize in Physiology or Medicine for 2017 has been awarded to three American scientists Jeffrey C Hall, Michael Rosbach of Brandeis University and Michael W Young of Rockefeller University for their discovery of the mechanisms controlling circadian rhythm. Jeffrey C Hall (now 72 years) obtained his doctoral degree from University of Washington in Seattle in 1971, was a post-doctoral fellow at Caltech during 1971 - 1973, and joined



Jeffrey C. Hall

Brandeis University in Waltham in 1974, remained associated with University of Maine since 2004 to 2012, initially as adjunct Professor and then as a Libra Professor of Neurogenetics. Michael Rosbach (aged 73 years), a contemporary of Jeffrey C Hall, completed his doctoral degree from MIT in 1970, was a post – doctoral fellow at University of Edinburg in Scotland, till, in 1974, he joined the faculty of Brandeis University, Waltham, USA. Michael W Young, aged 68 years now, received his doctoral degree from University of Texas, Austin in 1975; has been a post – doctoral fellow at Standford University, Palo Alto for next couple of years and then joined the faculty of Rockefeller University in New York in 1978. Alfred Nobel, (1833 - 1896), the man behind the prize wanted in his last will, dated November 27, 1895, establishment of a fund, the interest of which shall be annually distributed in form of prize to those who ..., shall have conferred the greatest benefit to mankind. In this context of giving greatest benefit to mankind, let us have a look at this year’s Nobel Prize in Physiology or Medicine. The discoveries will possibly enlighten discussions on almost mysteries been created



Michael Rosbach

around Sachin Tendulkar hitting a century against Kenya in a 1999 world cup match immediately on going back from India after his father’s sudden demise (time-zone transition in quick succession), major industrial disaster like Chernobyl (1986) and Exxon valdez oil spill(1989) possibly taking place due to alteration in

biological clock functioning because of shift work, influence of melatonin in alleviating Jet lag and so on.

The work and the implications: Hall Rosbash and Young have spent nearly three decades researching the biological clocks that regulate our bodies’ sleep patterns, metabolism, and response to disease; have discovered many



Michael W. Young

of the genes that regulate the circadian clock in the fruit fly *Drosophila melanogaster*, and have also studied the mechanisms that drive sleep and circadian rhythms in humans. The work has implications for the treatment of various sleep and mood disorders, as well as other dysfunctions related to the timing of gene activities underlying visual functions, locomotion, metabolism, immunity, learning, and memory. In 1984, Hall and Rosbash of Brandeis University and Young of Rockefeller University independently isolated a gene named *period*, first discovered in 1971 by Ronald J. Konopka and Seymour Benzer. The gene is needed to maintain circadian rhythm in the *Drosophila* brain, and its isolation led the three labs to subsequently unmask the general molecular mechanism for circadian clocks: a transcriptional feedback loop that progresses through the 24-hour cycle. Elements of the Young–Hall–Rosbash mechanism of the molecular clock were later found to be evolutionarily conserved throughout the animal kingdom. Hall and Rosbash initiated molecular neurogenetics studies of biological rhythms by analyzing the *per* gene. Through the 1990s, these investigations expanded to molecular and neurobiological experiments revolving round five additional rhythm-related genes in *Drosophila*, which were cloned [*timeless (tim)*] [*Clock (Clk)*, *cycle (cyc)*, and *cryptochrome (cry)*], and *pigment-dispersing factor (pdf)*]. To identify additional clock-related genes that contribute to the overall mechanism of circadian pacemaking, search was on. One way of detecting such factors has involved testing flies carrying transgenes in which they fused parts of clock genes to a reporter factor—firefly luciferase (*luc*); it allowed *per*- and *tim*-controlled molecular rhythms to be tracked in real time, in flies that are individually monitored for “glow cycling” over the course of several days. The initial fruits of *luc*-based screening for molecularly defective rhythm variants included two new mutations at the *tim* locus (which

confirmed the validity of the approach) and genetic identification of a novel chronobiological factor, *cry*. Hall and Rosbash began studies of *Drosophila* circadian rhythms almost 30 years ago, as an inter lab collaboration; their more short-term goal at that time was to clone the period locus, and more long-term goal was to define the machinery that underlies the almost ubiquitous process of circadian rhythmicity. The entry into the problem was the period gene (*per*) of *Drosophila melanogaster*. Their cloning and gene rescue efforts were published in 1984, but it wasn't until 1990 that some mechanistic understanding of circadian rhythmicity was achieved. Paul Hardin, a post-doc, discovered that *per* mRNA as well as its encoded protein (*PER*) undergoes fluctuations in level during the circadian cycle. These observations and others indicated that *PER* is important for a negative-feedback loop of gene expression and that transcription of the *per* gene itself is affected. As *PER* was shown to be nuclear, it was proposed that it rather directly inhibits the transcription of its own mRNA. Temporally controlled negative feedback at the transcriptional level is now an accepted feature of circadian timekeeping in mammals, plants, *Neurospora*, and even cyanobacteria. Moreover, *PER* as well as the many other clock components defined genetically over the past 10 - 15 years are largely conserved and perform similar functions in the mammalian clock. This indicates that the machinery as well as the principles of the *Drosophila* clock is widely conserved in animals.

Departure from recent trend: But more importantly, this year's award is a departure from the last few year's trend of recognizing works involving unraveling mechanism of diseases like cancer and Alzheimer's disease and like, to a work on a basic science issue. It is an honour for basic science research ie pursuing science for the sake of science. It probably seeks to reverse a recent trend of recognizing or funding research that focuses on works with obvious immediate benefits.

The fourth Awardee: Another interesting as well as significant fact is that the work has been carried out in fruit fly (*Drosophila melanogaster*) model. In the words of Jeffrey C Hall, it is the forth awardee! Possibly it will not be out of context to mention that we the humans must

learn to develop a culture of appreciating the crucial roles played by these small organisms silently. These are prolific breeders, have short generation time, and have only 4 pair of chromosome. And they are really giving benefit to mankind in deciphering the molecular mechanism of so many physiological and pathological phenomena; they have so far facilitated receipt of Nobel Prize for Thomas Hunt Morgan in 1933, Herman Muller in 1946 for the discovery of the production of mutations by means of X-ray irradiation, George W Beadle and Edward L Tatum in 1958 for their discovery that genes act by regulating definite chemical events. Muller and Beadle possibly belonged to the Morgan school and the trend continued with Edward B Lewis, Christiane Nusslein-Volhard and Eric F Wieschaus being awarded in 1995 for elucidating the role of key genes in development of fruit fly embryo. Another small organism to keep us alert in this regard is *C Elegans*; it is expected to increase its tally soon!

Not so encouraging Indian scenario! Although Indians or people of Indian origin have received the Nobel Prize for their contribution in different fields in last decade, the overall scenario within the country has not changed much. With Japanese obtaining degree from universities located within their country and/or working in Japan receiving the Nobel Prize, including one in literature in 2017, we are at best trying to shine in reflected glory of the fact that one scientist was a member of the research lab developed in Caltech in early 1970s and we are developing good fruit fly lab!

The award possibly points out that science cannot just remain confined to the domains of finding cure to cancer or AIDS and that too often in a sense to facilitate profit earning of select few. □

Shankarashis Mukherjee, PhD

Human Performance Analytics and Facilitation Unit

Department of Physiology,

University of Calcutta,

Rashbehari Shiksha Prangan

92 Acharya Prafulla Chandra Road, Kolkata 700 009

**msasish@yahoo.co.in*

ECONOMICS

The American economist Richard H. Thaler, who received the Nobel Prize in Economics this year for his contribution in behavioural economics, is a pioneer in behavioural economics, a research field in which insights from psychological research are applied to economic decision-making. A behavioural perspective incorporates more realistic analysis of how people think and behave when making economic decisions, providing new opportunities for designing measures and institutions that increase societal benefit. Economics involves understanding human behaviour in economic decision-making situations and in markets.



Richard H. Thaler

People are complicated beings, and we must make simplifying assumptions if we are to build useful models. Traditional economic theory assumes that we can always execute our plans and that we only care about personal gain. This simplified model of human behaviour has helped economists to formulate theories that have provided solutions to important and complicated economic problems. However, the discrepancies between theory and reality are sometimes both systematic and significant.

Richard Thaler has contributed to expanding and refining economic analysis by considering three psychological traits that systematically influence economic decisions – limited rationality, perceptions about fairness, and lack of self-control.

Limited Rationality

It is not realistic to assume that people, before each economic decision, consider every feasible alternative and all its long-term consequences. This is quite simply an insurmountable task, so decisions are often taken using a narrow focus. Economics Laureate Herbert Simon developed the concept of bounded rationality – limited rationality – as a collective term for organisations' and people's cognitive limitations and simplified decision-making rules. One example of such limitations is found in Richard Thaler's theory of mental accounting, which describes how people organise, formulate, and evaluate financial decisions. We tend to simplify such decisions by creating separate accounts in our minds, making individual

decisions on the basis of their effect on each of these accounts rather than on our total assets. One example is how many people divide their household budget into one account for household bills, another for holidays, etc., with rules that prevent using money from one account to pay for something in another. This behaviour sometimes leads to extra costs, such as not using money from long-term savings accounts for short-term needs, instead taking out expensive consumer loans. At the same time, this can help us to plan our finances and protect long-term savings. Another element of mental accounting is that we use reference points to help us make decisions.

In his research, Thaler has provided numerous examples of how mental accounting using differing reference points may lead to decisions that appear strange when evaluated from a traditional economic perspective. One example is a consumer who finds out that the watch she is about to buy is 100 Swedish krona cheaper in another shop. She chooses to go to the other shop if the watch costs 1,000 krona but won't do so if it costs 10,000 krona even though the saving in krona is the same. The explanation is that she focuses on the percentage, rather than on the actual saving relative to the reference point.

Other factors that govern our decision-making are previous experience and our perceptions of ownership itself. We normally want more money for selling something we own than we are prepared to pay in order to buy exactly the same item – a phenomenon that Thaler calls the endowment effect. The endowment effect can have long-term consequences, such as reducing trade in goods and services and making legal disputes more difficult to resolve. Thaler's explanation for the endowment effect is based upon how people tend to experience the negative feeling of a loss more strongly than the positive sense of an equally large gain, known as loss aversion. Giving up something we already own is experienced as a loss, while acquiring the same thing is experienced as a gain. To manage the many financial decisions in our lives, we often organise them in separate accounts in our minds. The theory of mental accounting demonstrates the unintended problems that may result. More generally, what we define as a gain or a loss depends on where we place the reference point, which is therefore important for our decision. For example, discount sales make consumers place the reference price higher than they otherwise would, and they thus perceive a purchase as a better deal than if the item was sold at the same price but not in a sale. Another example is that an investor in the stock market does not define a deal as a

profit or loss until the shares are actually sold. This leads to investors generally holding on to losing shares for a long time in the hope that “it’ll get better”, and selling winning shares too soon in order “to bring home the profit”, despite it often being more advantageous to do things the opposite way (for tax reasons, for example).

Our own experiences also influence the risks we are willing to take. Someone who has recently gained money on the stock market or at a casino tends to take greater risks than someone who has recently lost money. It is less painful to lose if we are still “in the black” in our mental account, even if circumstances are otherwise the same (something Thaler calls the house money effect).

Social Preferences: What is Fair?

When making decisions, people not only take what is beneficial to themselves into account. They also have ideas about what is fair, and they can consider other’s welfare in both a positive way – through cooperation or solidarity – and a negative way – such as through jealousy or malice. Large-scale experiments conducted by Richard Thaler and other behavioural economists, have shown that notions about fairness play a major role in decision-making. One frequent objection is that results from laboratory experiments cannot be transferred to real life, but it is easy to find examples where fairness considerations have an impact outside the laboratory. Unexpected rain can create an unexpectedly high demand for umbrellas, but if a shopkeeper then raises their price to match the high demand, many consumers react negatively and feel that the shopkeeper has behaved greedily. Companies that contravene fairness norms may be punished by consumer boycotts, which may get them to maintain their prices in cases where they would otherwise have raised them. Additionally, there are strong feelings about what is fair when it comes to pay, which affects wage setting on the labour market through comparisons between different employee groups. It is difficult to gain acceptance for nominal pay cuts – their current salary level is the given reference point below which people do not want to drop – while it is easier to accept a nominal wage increase that is lower than inflation, even though this entails a pay cut in real terms.

Short-term Temptation Against Long Term Gain

One of the problems that common people suffer from and entangled in a dilemma at all levels of our life to get rid of short-term temptations that threaten long-term wellbeing. This could be food and drink, smoking, consumption, saving for distant goals, or post-retirement

planning. A person who chooses a longer education has a lower income during their studies, but can in return look forward to benefits in the future. Experiences that are close in time take up more of our awareness than those that are further off; a thousand krona next year is perceived as worth less than a thousand krona today, regardless of whether it is an income or an expense. In traditional economic theory this is described using discounting – the assumption is that both income and expenses reduce by a constant factor with every passing month or year. Using such an assumption, the ranking of two future alternatives will always remain the same. However, it is possible to change your mind when choosing between two options. The explanation is that experiences that are close in time take up more of our awareness – we discount more rapidly early on. Richard Thaler has, together with HershShefrin, created an alternative model for describing the dilemma caused by the internal tension between a planning self and a doing self (planner-doer). The planning self thinks and makes decisions with the aim of long-term happiness, while the doing self is governed by more short-term goals. This division has been adopted in modern psychology and is also supported by recent research in neuroscience. The solution to the dilemma is often about helping the planning self in some way, by removing short-term courses of action. This deviates from traditional economic theory, in which more potential courses of action are always better than fewer. In some cases, people manage to exercise restraint without help – mental accounting can, for example, be a way of avoiding short-term extravagances. In other cases, society may need to help the planning self by designing regulations and institutions that encourage ecogniz that has a longer-term perspective.

Behavioural Economics in Practice

Behavioural economics has also questioned rational ecogniz as it applies to areas such as financial markets. Richard Thaler, along with Laureate Robert Shiller, established the research area of behavioural finance, in which researchers have documented apparently unjustified market volatility that seems incompatible with the theory of effective markets. Thaler has also documented what amounts to negative market values for shares – which is unreasonable, because you can always discard a share that has no value. Experiments with test subjects who can choose between different investments show that people are sensitive to the choice of time horizon. Investors tend to prefer low-risk securities over short time horizons, but when they are presented with the potential results of various investments over a longer time horizon, they are more likely to choose higher risk securities, such as shares. Common

marketing practices can be understood as taking advantage of consumer irrationality. Discounts or exhortations of the type “buy three, pay for two” give consumers a sense of having gained and so move the reference point for evaluating the price. Lotteries and betting are marketed through overexposing the rare winners and covering up the multitude of losers. Many consumers are lured into taking loans with disadvantageous terms so they can buy an item they cannot actually afford. Thaler’s research is frequently cited in marketing literature and his insights, and those of other behavioural economists, can help us recognize marketing tricks and avoid unfavourable economic decisions.

Research in behavioural economics can be used by politicians and other decision-makers to design alternatives

that provide benefits to society. Richard Thaler and Cass Sunstein have argued that, in more areas, both public and private institutions should actively (but with maintained freedom of choice) try to nudge individuals in the right direction. Among other things, this has led to the introduction of nudge units in several countries, including the UK and the USA, agencies that aim to reform public administration through the use of behavioural economic insights. Improvements often involve simple things, such as how the default option is defined – the one that is the result unless you actively choose something else. There are applications in fields such as pension savings, organ donation and environmental policy. □

Source: www.kva.se

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