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The Science Magazine of the Max Planck Society

FOCUS
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New Beginnings in the Cafeteria

Two men, one word: On February 26, 1948, Otto Hahn (right, standing) and Lower Saxony’s Minister of Cultural Affairs Adolf Grimme seal the foundation of the Max Planck Society. High-caliber scientists, including several Nobel laureates, attended the event. The gathering took place in the fellowship house of the dismantled Aerodynamic Research Institute in Göttingen. Such were the modest beginnings of the successor organization of the tradition-rich Kaiser Wilhelm Society. The rustic rooms, however, still serve as a venue for gatherings today: the place where venerable men came together at simple wooden tables more than 60 years ago to open a new chapter in Germany’s research history is the place where the staff of the Max Planck Institute for Dynamics and Self-Organization gather today to enjoy their lunch together.
Regulating signal: The amino acid sequence of a protein that plays a role in regulating genes.

**FOCUS**

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As the physician Hippocrates taught us, “It is more important to know what person the disease has than what disease the person has.” Today, 2,400 years later, science is revisiting this tenet: our understanding of the genetic differences between individuals will soon provide a basis for personalized medicine. After all, around 30 to 80 percent of patients today derive no benefit from the medications they are receiving for a range of common conditions – some drugs and certain doses are actually hazardous for individual patients. There is no question that a paradigm shift toward specific, evidence-based and personalized medicine would be a great step forward.

Doctors are already able to choose specific drugs based on the patient’s gene variants. The discovery that certain gene variants affect the way in which an individual responds to the components of a drug is itself an important addition to our knowledge. This has given rise to a new area of research: pharmacogenetics or pharmacogenomics, which aims to harmonize drugs and dosages with the patient’s genetic profile. There are known genetic variants that affect the way patients respond to cholesterol-reducing drugs, anticoagulants, AIDS treatments, antidepressants and other common prescription drugs.

New diagnostic procedures also allow us to step up the fight against cancer. The basis lies in molecular genetic studies of the tumors themselves. A prime example of this form of personalized medicine is Herceptin – a therapeutic antibody used by doctors to treat a certain form of breast cancer. One of the defining features of these tumors is that large quantities of the protein HER2 are produced on the surface of the tumor cells, stimulating cell growth. Herceptin can interrupt the protein function and thus also the growth of the tumor.

At the same time, it also activates the body’s own immune cells in order to kill off the cancer cells.

The active ingredient is the product of research by Axel Ullrich, Director at the Max Planck Institute of Biochemistry in Martinsried. In the meantime, other approaches to the treatment of cancer are adopting his model, which combines molecular diagnostics and therapy.

The hope that decoding the human genome would lead directly to rapid progress in the field of medicine has, as yet, barely been fulfilled. The number of monogenetic diseases – those that derive from a defect in a single gene – is comparatively small, and the diseases themselves quite rare. Most widespread diseases are associated with multiple genetic mutations.

In addition, genetic regulation and a number of environmental factors play an important role in the way diseases manifest themselves. However, it is known that specific genetic variants increase the risk of contracting some chronic illnesses, such as coronary heart disease, diabetes and Alzheimer’s. Corresponding studies may provide a basis on which to develop preven-
tive treatments for patients with a disposition toward certain diseases.

Still, if we are to derive a sustainable prognosis from an individual genome, there are other factors that science must be aware of. It is a matter of aligning the genomic data with the phenotype, that is, the various features of the organism concerned. Genomic and genetic testing procedures must be supplemented by technologies with the ability to create molecular fingerprints, such as transcriptome, proteome and metabolome analyses.

In practice, the new methods raise many questions – as in the case of individual genome sequencing, which, in less than two years, is likely to be available for only USD 1,000: Do companies adequately protect their clients’ genetic data? Do they accept liability for false prognoses and misinterpretations? A legal framework for such tests is thus far lacking in Germany. There is also a lack of mandatory standards for the approval of predictive tests and, so far, no obligation to provide any details of the potential capabilities and limitations of the services offered.

Overall, the issue needs to be addressed by the legal system: there are questions of genetic privacy to resolve, such as a right to data protection and self-determination for those who are genetically at risk. The ability of health and pension insurers, employers and other potentially interested parties to access such data must also be addressed.

Politicians must initiate a public debate on the questions raised by personalized medicine. Do we actually want to know about our genome and our molecular characteristics? Are we willing to disclose this information? Do we want a glimpse of our own medical future? Are we ready to adapt our lifestyle to our genome? Do we want to lead a biologically planned life? All of these questions have to do with how we see ourselves. They touch on both legal and fundamental ethical aspects of our existence.

We must also ask how medicine itself should approach these new possibilities: these methods have found few specific applications in clinical practice to date. Their use on a broad scale will be determined by clinical success. If doctors are to correctly interpret diagnostic techniques based on molecular markers and initiate appropriate treatments, molecular genetics and systems biology must become part of medical training. In addition, in their conversations with patients, doctors must take a far more individualized approach and explain in detail their interpretation of molecular genetic diagnoses and the consequences.

In short, the human factor will play a greater role in personalized medicine – especially in matters of disease prevention, in which the personal responsibility of the individual plays a major role. Should there – dare there – be an “obligation to be healthy”? The social sciences could be helpful in this context.

It is also necessary to verify how effective the new methods are, and how they work in comparison with conventional treatments. Only then will doctors, patients and health insurers be in a position to decide how viable molecular medicine is in practice and whether it can lead to genuine improvements. Experts must ask themselves how much added value their approaches and methods of personalized medicine actually deliver for the patient and for society as a whole.

Medicine is experiencing a paradigm shift from healing the sick to predicting and preventing disease, but there is still a way to go. Hippocrates made another far-sighted recommendation: “Guide the healthy with care to preserve them from disease.”

Peter Gruss, President of the Max Planck Society
Max Planck Research Award 2010

The prize of 1.5 million euros goes to Sebastian Thrun and Bernhard Schölkopf

Intelligent systems can optimize themselves in such a way that they can operate successfully in a changing environment. Sebastian Thrun teaches and researches at Stanford University. His main interest is robotic systems that are able to learn and move independently. Thrun was able to demonstrate that it is possible to use a mobile robot to create a map of the surroundings without the availability of prior knowledge, and to effectively estimate the robot’s position and orientation. In 1997, he developed the robot called “Rhino,” which was capable of providing a guided tour of the Deutsches Museum in Bonn. The findings of Thrun’s research have also been used in the development of autonomous vehicles. Intelligent driver-assistance systems are designed to reduce the number of road fatalities and help traffic flow more efficiently. “Stanley,” the driverless SUV developed by his team, covered a distance of more than 125 miles of rough terrain across the Mojave Desert in 2005. Seven test cars are currently navigating California’s road system and have already traveled more than 125,000 miles. These vehicles can detect their surroundings using laser scanners and cameras, and respond to any situation in accordance with the relevant traffic regulations.

Bernhard Schölkopf is a Director at the Max Planck Institute for Intelligent Systems in Tübingen and one of Europe’s leading researchers in machine learning. He researches computational methods, known as algorithms, that can be used to program computers to enable them to respond flexibly to new situations. Schölkopf’s research findings have made algorithms for machine learning more efficient. For example, he analyzed and considerably expanded knowledge of support vector methods, which can be used to help computers recognize faces in photos more quickly. He has also found a way to work with far fewer support vectors, which simplifies the decision about whether a segment of a photo contains a face. This means that photos can be analyzed 30 times faster than with an analysis using all of the support vectors. Support vectors can also be used to identify genes. The genetic profiles of patients with known diagnoses are also examples of where an algorithm can predict the diagnosis of patients with different genetic profiles.

Zoo Turned Ark

Max Planck researchers urge greater role for zoos

Zoological gardens are somewhat controversial. In particular, animal rights activists criticize them for keeping animals in conditions that are not suitable for their species. “Zoos play an important role in conserving threatened species,” emphasize Dalia Conde and Alexander Scheuerlein from the Max Planck Institute for Demographic Research in Rostock. A study carried out by the researchers shows that zoos house 20 to 25 percent of threatened mammal species, 9 to 18 percent of threatened bird species and 18 to 50 percent of threatened reptile species. Zoos offer animals a refuge until they are ready to survive in the wild again and can be released into their natural habitats. The researchers are calling for the establishment of specialist zoos that focus on the breeding of just one or a small number of species, with the aim of increasing breeding success. Examples of animal species whose risk status has been downgraded thanks to zoological gardens are the Asian wild horse (Przewalski’s horse) and the Californian condor.

(Zeit, March 18, 2011)
Living on the Edge

Experts from all over the world meet in Berlin at the 4th Max Planck Symposium: “Life under extreme conditions”

Over the course of evolution, almost everywhere on our planet has been colonized – even those places considered to be extremely hostile to life. Microorganisms live in boiling volcanic water, for instance, as well as in cold marine sediment hundreds of meters thick in the depths of the oceans. As John Parkes from Cardiff University reported, their distribution and activity there depends on environmental factors and their access to certain energy sources. According to Peter Girguis of Harvard University, however, some enter into symbiotic relationships and, in this way, make themselves independent of external energy sources, operating their own power plant as it were. Microorganisms such as halobacteria have developed particular strategies in order to survive extremely high salt concentrations like those that prevail in salt ponds or in the Dead Sea. Dieter Oesterhelt summarized the results of decades of research carried out at the Max Planck Institute of Biochemistry: these microorganisms manage to survive in such extreme conditions thanks to an appropriate membrane structure and a special form of breathing. Both vertebrates and invertebrates can also make inroads into extreme areas. For example, as Arthur deVries from the University of Illinois reported, fish in Arctic waters virtually produce their own natural antifreeze protection. These extraordinary abilities of organisms are very interesting for basic research, as the limits of their ability to adapt can be traced back to the properties of life’s building blocks. However, they also yield potential innovative technical applications. For example, bacteriorhodopsin, a protein pump in the membrane of halobacteria first described by Oesterhelt and his team, is also suitable as a recording medium in holography, and a patent was filed for it in 1991.

Southern Sudan – Fit for the Future

Max Planck researchers in Heidelberg involved in drafting transitional constitution

In a referendum held in January 2011, an overwhelming majority (98.83 percent) of the Southern Sudanese population voted in favor of an independent state. At a conference held in Heidelberg from March 8 to 12, 2011, Southern Sudanese legal experts and parliamentarians, together with international experts, drafted a transitional constitution under the guidance of Rüdiger Wolfrum. According to Wolfrum, it was clear from the consultations that there was a desire for a structure based on the rule of law and democracy. As there was not enough time for a comprehensive constitutional process before the country became independent in July, a transitional constitution was drafted. A key element in the foundation of a state is the creation of a constitutional framework, guaranteeing that the new state is based on democracy and the rule of law. The subject of future dealings with Northern Sudan, particularly in relation to issues such as state succession, future citizenship, the sharing of natural resources and the cross-border movement of nomads, was also on the agenda. The Max Planck Institute for Comparative Public Law and International Law has been actively involved in a number of projects in Sudan since 2002.
Intelligent Systems in Stuttgart

New direction for Max Planck Institute for Metals Research

The new focus of research includes computer science and biology, as well as the areas of materials research that were already established at the institute. In addition to the Stuttgart location, a new division of the institute is under construction in Tübingen. Each site will have four research departments. The German federal state of Baden-Württemberg has allocated special financing of 41 million euros for the project. Along with a new research direction, the institute will also get a new name: The Max Planck Institute for Intelligent Systems. The Founding Directors include Bernhard Schölkopf, previously a researcher at the Max Planck Institute for Biological Cybernetics in Tübingen, Joachim P. Spatz from the Max Planck Institute for Metals Research, and Michael J. Black from Brown University, USA. Black’s appointment brings one of the world’s leading experts in machine vision to the helm of the new institute. The computer scientist took up his position in Tübingen on January 1, 2011. Other appointments will follow.

The new institute has a globally unique selling point: it is the first institution ever to accommodate, under one roof, software and hardware expertise in three key aspects of intelligent systems: perception, learning and action. Machine learning, image recognition, robotics and biological systems will be studied in Tübingen, while “learning material systems,” micro- and nanorobotics and self-organization will be explored in Stuttgart. Although the focus will be on basic research, there is also great potential for practical applications at the institute, for instance in robotics, medical technology and innovative technologies that are based on new materials.

Benefits of the Genetic Material Data Flood

Max Planck Institute for Molecular Genetics coordinates European infrastructure for sequencing and genotyping

The European Sequencing and Genotyping Infrastructure project (ESGI) is coordinated by the Max Planck Institute for Molecular Genetics and will be funded for four years as part of the EU’s Seventh Framework Programme. The project brings together researchers from Austria, Spain, France, Germany, Sweden and the UK. ESGI aims to consolidate Europe’s position as a world leader in genetics, genomics and molecular biology. Research infrastructures are crucial in ensuring that scientists reap the greatest benefits from the huge quantity of data that is generated every day. For example, sequencing a genome previously took years; now it can be done in a matter of hours. The flood of data generated in sequencing and genotyping experiments must be managed cooperatively, as no single institution working on its own can handle such masses of information and simultaneously keep up with evolving technical challenges.

ESGI partners are focusing their attention on integrating and standardizing current and emerging technologies. “The infrastructure is designed to expedite research in the life sciences in Europe,” explained project coordinator Sascha Sauer. ESGI aims to make it possible for scientists across all disciplines to use emerging technologies to decipher the complex functions of genes in a cost-effective way.
Take a Bow!

Max Planck Society's press office awarded two prizes

Together with colleagues from the Max Planck Institute for Evolutionary Anthropology in Leipzig, the press office at the Max Planck Society has won the idw’s first prize for scientific communication. The prize is awarded in recognition of press releases published in the idw in 2010 “that are marked by their professionalism (quality), outstanding news value (relevance) and scientific importance (originality).” The MPS received its prize for the press release dated May 6, 2010 entitled “The Neanderthal in Us”. idw (Informationsdienst Wissenschaft e. V.) is one of the most important Internet platforms for news from universities and the scientific community in German-speaking countries, and includes around 850 scientific facilities among its members.

MaxPlanckResearch also scooped up a prize: the Max Planck Society’s research magazine was presented with an “Award of Excellence” as part of the first International Corporate Media Award. A total of 194 publications from seven countries were submitted. MaxPlanckResearch’s contribution impressed “with the manner in which the magazine utilizes images. Abstract contents were illustrated very well. In addition, images showing scientists within the context of their research work were well chosen and integrated into the page layout. MaxPlanckResearch provides an excellent overview of the broad spectrum of the Max Planck Society’s field of activity,” the jury found.

Science – communicated superbly: The Max Planck Society received first prize from the idw for a press release.

Science – illustrated superbly: MaxPlanckResearch received the „Award of Excellence“ for its visual merit.

On the Net

Birthday Podcast for Feodor Lynen
Feodor Lynen, winner of the Nobel Prize for Medicine in 1964, would have been 100 years old this year. The biochemist deciphered the role of activated acetic acid in fatty acid metabolism and laid the foundations for the development of drugs to fight arteriosclerosis and excessive blood cholesterol. A new podcast (in German) in the “Echt nobel” (Truly noble) series recalls this extraordinary scientist: www.mpg.de/1330934/Feodor_Lynen

Focus on People
The intellectually curious will have the opportunity to go on a voyage of discovery on the island of Mainau between May 20 and September 4, 2011. Visitors to any of the 20 pavilions will be amazed at the experiments, simulations and exhibits on the subject of health. The exhibition, in which the Max Planck Society is once again involved, provides schools with a broad range of activities and workshops, such as a “health rally.” Take a virtual tour of the pavilions at: www.mainau-entdeckungen.de

Patent Twitter
Markus Berninger, who works at Max Planck Innovation in Munich, tweets about inventions, patents and the transfer of technology and knowledge at the Max Planck Society. His Twitter streams (in English) are very popular and he quickly acquired more than 1,300 followers in science and industry: www.twitter.com/MP_Innovation
Robust Financial Markets – Something to Bank On

Greece, Ireland and Portugal avoided bankruptcy only due to a bailout by the European Union and the International Monetary Fund. The stability of the European Monetary Union hangs in the balance. Since the onset of the crisis, experts have debated new sanctions, the establishment of a monetary fund and other institutional possibilities. Yet it is not the rules that are at fault, our author believes, but a failure to apply them properly. Thus his call for more trenchant reforms of the banking sector and financial markets.

TEXT KAI A. KONRAD

The focus of attention is shifting to the role of creditors

would have thought that, in the space of one weekend, the European Union, in concert with the International Monetary Fund, would agree to spread a $750 billion euro safety net for insolvent members, blatantly ignoring Article 125 of the treaty that defines how the European Union should function? Who would have thought that the European Central Bank would ever become a bulk buyer of dubious sovereign debt, then promptly move to increase its subscribed capital?

Europe’s political reactions, too, were something to behold. On September 7, 2010, the Council of Ministers discussed the introduction of the “European Semester,” to commence in 2011. The Semester, which begins in March each year, is essentially a cycle of consultation in which member states are required to submit their national budgets for the following year for discussion at the European level—with the participation of the Commission and the Council. At a summit on September 29, 2010, the European Commission then presented plans for a wide-ranging reform of the European Union’s financial constitution. The Commission proposed to tighten the supervisory and disciplinary measures of the Stability and Growth Pact and make potential sanctions against debtor states a more automated consequence. It also created an entirely new system of supervision, intervention and sanction, the function of which would be to diagnose, deter or punish possible macroeconomic imbalances within individual member states. In May 2011, the Council of the European Union made the decision to expand the safety net by additional hundreds of billions of euros, and to perpetuate this safety net and rename it the European Stability Mechanism (ESM). Some observers already consider the ESM to be the precursor to

This article is largely based on ideas outlined in “Schulden ohne Sühne? Warum der Absturz der Staatsfinanzen uns alle trifft,” a book by Kai Konrad and Holger Zschaepitz that was completed in May 2010. The article is a modified version of a contribution that appeared in WIRTSCHAFTSDIENST (Vol. 90(12), 2010).
European government bonds. Simultaneously, it was decided to reform the treaty, making the euro and its survival a European policy goal. This treaty reform can be seen as a major change in European governance, as it potentially opens the door for many future policy measures.

Apart from these far-reaching resolutions, there are myriad other considerations occupying the political space. How are these initiatives to be assessed in light of the past ten years of experience with the European Stability and Growth Pact? Can these resolutions overcome the central problems of credibility that have, in the past years – but especially in 2010 – prevented important pages of the rule book from being applied? And if the answer to these questions is clearly no, what would the correct political response be?

Many observers blame the failure of the Stability and Growth Pact on an absence of transparency and a lack of political appetite to implement the rules of the Pact. Thus their call for the rules to be reformed: more transparency and more prevention will, they hope, facilitate prompt reactions to possible fiscal misdemeanors. Existing political voting mechanisms, it is argued, should be replaced by rigid rules and the automated imposition of sanctions on those who break them. Preventive monitoring of individual budgets (the European Semester) is intended to allow early intervention before the (mis)deed is done – and long before an imbalance occurs. More transparency and prevention would have revealed Greece’s financial plight at an earlier stage. It would then have been possible, so the argument goes, to put Greece back on a sustainable financial course.

Automated mechanisms in place of political majority decisions are justified by the argument that, in the past, “one culprit has been voting on sanctions against another.” In that position, there was insufficient incentive for sanctions to be imposed. The result would actually have been to compound the fiscal wrongdoing, insofar as culprits running up excessive deficits would be confident that there would be no political majority in favor of punishment. Automated mechanisms would not suffer from this credibility problem.

There may be a kernel of truth in these arguments. However, one cannot hope to render the Stability and Growth Pact both credible and functional by these measures. It was not fundamentally an absence of information about just how unsustainable the budgetary policies pursued by individual member states actually were that led to Europe’s sovereign debt crisis.

Even according to the official statistics – which have themselves lately been strongly criticized – Greece exceeded the 3 percent threshold for net government borrowing in nine out of ten years since it joined the euro zone. These infringements were not a state secret. The situation may have been made worse by the financial and economic crisis, but it had been developing in plain sight over many years.

Even under the kind of supervision envisaged by the European Semester that has now been adopted, states can appear to be treading a path of financial sustainability while still heading deeper and deeper into debt. A government that is resolved to continue to run up debt, and that has the support of broad sections of its own population in doing so, will still have the means despite the European Semester. There are few limits when it comes to dressing up the balance sheet.

Selling public buildings at high prices, then leasing them back at excessive rents, or taking out loans via public undertakings that are themselves backed by state guarantees are just two examples of a whole class of concealed arrangements by which a government can take on additional debt that bypasses the official budget. And this kind of debt is generally more expensive than openly declared government borrowing.

Given these possibilities, even a far more comprehensive and penetrating system of monitoring national budgets than the one enacted by the EU would have little chance of success. It would, however, have an unwelcome side effect: if, despite intense supervision and restrictions on individual autonomy, a member state were to find itself in dire budgetary straits, the debtor would have good reason to demand that the European community come to its aid: as long as the debtor is only doing what
the other states demand, and its actions are subject to strict rules, provided that it is in formal compliance, the others cannot very well claim that it alone is responsible for its actions. The example of Ireland’s impending insolvency in November 2010 showed that adequate transparency in matters of budgetary policy is not sufficient to avoid extreme imbalances. Ireland’s deficit was not especially conspicuous. It was rather the case that the country came to grief as a result of the guarantees it gave for the Irish banking sector – a measure that would not necessarily have fallen foul of a system of prevention, or attracted automatic sanctions.

So what can one expect of automated sanctions? Can it be hoped that such sanctions will constitute a credible threat of punishment for fiscal misdeeds, and as such, have a disciplinary effect on individual states? Or will automated mechanisms ultimately fail to act as a credible deterrent?

In fact, the experience of the past ten years already hints at an answer to the questions. The Stability Pact, in its pre-reform version, already provided for a range of automated mechanisms that were later deactivated. Consider the intervention by the German government in 2002, which initially prevented the implementation of an entirely automated delinquency procedure. A more dramatic and more important example of the failure of automatic rules is that of the safety net installed in May 2010: the “no-bailout clause” in Article 125 was fundamentally conceived as an automated mechanism.

The rule states that if a euro zone member state should find itself in extreme fiscal difficulties, neither the community of states nor any individual member state is required to provide financial assistance. Publicly and politically, the rule has predominantly been interpreted as “shall not provide assistance.” However, this automatic no-bailout mechanism did not prevent the euro states from flouting the rule book.

There has been broad speculation as to why, in May 2010, the European Union and the International Monetary Fund spread out a 750 billion euro safety net as a mechanism for inter-state assistance. At any rate, large parts of the political community were concerned that, following Greece, other euro zone countries, too, would soon find themselves in a situation in which it was practically impossible to refinance their borrowings on the capital markets. By putting this rescue plan in place, the politicians hoped to avoid this chain of events. Above all, however, there was widespread fear that, if one or more of these states were forced to restructure their debt, the result would be to throw the financial markets into disarray and trigger insolvencies among major financial institutions of systemic importance.

Given the possible negative consequences, Europe found itself in what is known as the “Samaritan’s dilemma.” As applied to the relationship between the euro states, the situation was essentially as follows: while there was no deep bond of attachment or altruism between these states, it was in the interests of the richer among them to assist those on the periphery in order to avert the consequences that such a debt restructuring would have on their own banking sectors.

The expectations of assistance, including the possibility of long-term inter-state transfer payments, proved to be a harmful incentive both among the states and on the government bond markets, insofar as they implied joint liability on the part of the euro zone countries. Holger Zschäpitz and I described the consequences in our book _Schulden ohne Sühne?_ In such a situation of shared liability, states have too little incentive to save and consolidate – something that also applies even to states that are repeatedly seen as riding to the rescue. One of the few credible ways for such states to cast off the mantle of rescuer is to run up high levels of debt of their own.

What’s more, the buyers of government bonds cease to have any incentive to verify the creditworthiness of individual countries and to respond to any deterioration by exhibiting a reluctance to buy. If they are going to get their money back come what may, there is no need for them to distinguish between lending to states of sound or unsound financial standing. Consequently, if a member of the community of states over-borrows, it impacts the creditworthiness of the community as a whole. Refinancing costs rise for every member of the community.
In fact, the costs borne by one small member state are only a fraction of the added expense caused by its own over-indebtedness. The bulk of the burden is shouldered by the other states. This, too, can lead to fundamentally excessive borrowing on the part of every individual state.

The political effects of this Samaritan’s dilemma for “Project Europe” may prove to be more significant than even the impact on bond markets and on the budgetary policies of member states. Repeated aid payments or extensive transfers from richer to poorer members that could well extend over many years and assume substantial proportions are likely, in the long term, to lead to political tensions between donors and recipients.

The rescue package for Greece has already given us a foretaste. In Germany, for example, the Greeks were frequently branded as lazy tax dodgers. The perception that Germans were expected to tighten their belts in order to send money to Greece was not especially popular. The discussion was dominated by news reports citing uses to which the money would be better put in Germany rather than sending it to Greece. At the same time, voices were raised in Greece calling for Germany to make reparations for World War II, even if no official demands were forthcoming.

The potential for such a situation to blow the European Union apart is considerable. There are signs of a dividing line being drawn in Europe between those states with sound finances and those whose financial position is less sound. In view of Europe’s history, it is unlikely that Germany will take the first step toward abandoning monetary union. It is, however, conceivable that some states will draw their own conclusions.

In addition to the international tensions that might develop as a result of inter-state transfers, a European Transfer Union would also have the potential to ignite radicalism in individual countries. Slogans such as “Saving for Greece? No thanks!” could inspire populist movements on both ends of the political spectrum. Were radical populists to accede to government responsibility on the back of this issue, the result could be to trigger potential splits within the European Union.

So what is the right thing to do? How do we extricate ourselves from this dilemma? The Advisory Committee to the German Federal Ministry of Finance outlined an answer in a letter to the Minister in the summer of 2010. The Committee advised that Europe’s financial constitution should be left untouched. With an independent Central Bank, a procedure for budgetary supervision (Article 126) and, above all, the no-bailout clause in Article 125, there are already excellent rules in place. If they were to be complied with, these rules would be adequate to ensure price stability and sustainable budget policies. It is not the existing rules that are at fault, but failings in their application.

The fact that the no-bailout clause was set aside by political resolutions has less to do with the rules themselves than with the institutional context in which decisions are made on how to apply them. Therefore, when it comes to reform, the central question is: Which factors in the institutional environment were principally responsible for deactivating the automated no-bailout mechanism? We must then ask how these factors can be altered.

One of the central reasons for not applying Article 125 and proceeding instead with a financial rescue, first for Greece and later for Ireland and Portugal, is the state of the financial markets: as long as politicians fear the market turbulence and bank-

Revised by the financial constitution should be left untouched

ing sector insolvencies that restructuring the debt of a euro zone country would entail, no restructuring will take place – even if it were the economically correct and necessary thing to do. If the no-bailout clause is to be upheld in the future, then rather than reform the Stability and Growth Pact, the true reasons for why the no-bailout clause was overruled need to be addressed. This implies more trenchant reforms of the banking sector and the financial markets.
Debt restructuring means putting a partial block on the repayment of sovereign debt, followed by negotiations between government and creditors regarding the terms of repayment. This is by no means a pleasant event for the financial markets, given that the holders of government bonds will forfeit some of what they are owed. (A clear distinction should be drawn between debt restructuring and an exit from the euro zone: the one does not entail the other, even though, unfortunately, the two are often confused in the economic policy debate.)

An adequately robust banking system that is properly provided with equity, and in which banks do not build large unbalanced positions in the bonds issued by any one individual state, but instead divide their investments between a balanced variety of asset classes, can survive the write-offs resulting from restructuring the debt of a euro zone country relatively unscathed. Banks with a sufficiently conservative investment strategy can accommodate such write-offs without getting into difficulties themselves.

To imagine banks and financial markets in such a robust state is not utopia. On the contrary, this is a situation in fundamentally stable balance: in a financial world in which all banks and financial institutions are well provided with equity and pursue a conservative investment strategy, there needn’t be an incentive for any individual among them to deviate from such a strategy. One or another might attempt to build huge and risky positions, betting on a specific event, as may even be common practice in the current financial market situation.

In view of the behavior of the other banks and their equity capital, however, this would be a dangerous course of action for both the institution and its shareholders. Given the robustness of every other bank, the transgressor that over-reached itself would simply go under. Unlike the present situation, the government would have no need to launch a rescue since, in a sufficiently resilient financial world, the individual bank would not be a systemic risk.

Robust financial markets with banks whose shareholders bear responsibility for possible investment losses and that are not in need of being saved at any cost are desirable for many other reasons, too. A sufficiently strong financial market system might even save the world from future financial crises and their attendant impact on the economy.
Unraveling the Tangled Tau Web

Particle accelerators do not automatically spring to mind as a tool for use in Alzheimer’s research. However, the German Synchrotron Research Center (DESY) in Hamburg has provided invaluable service to Alzheimer’s researchers Eva-Maria and Eckhard Mandelkow from the Max Planck Research Unit for Structural Molecular Biology. With DESY’s help, the Mandelkows have succeeded in illuminating the processes that lead to the memory loss associated with Alzheimer’s disease. Their research findings raise great hopes for the development of effective treatments.
A constant humming can be heard throughout the complex. Metallic, not very deep, distinct – the noise is generated by the power supply to giant magnets. These are required to deflect the electrons propelled at an unimaginable speed through the storage rings of the DESY, DORIS and PETRA 3 particle accelerators, a process that can tease out vast numbers of protons from matter. When focused, these protons generate a very bright, energy-rich beam that can be used, for instance, to examine proteins in minute detail. Every year, 3,000 guest researchers from all over the world come to DESY in Hamburg for this very purpose.

Unlike their international colleagues, Eckhard and Eva-Maria Mandelkow are permanently based at the source. They work with DORIS, which the two scientists, who have made an enormous contribution to shining light on the darkness surrounding the cause of Alzheimer’s disease, describe as the “ultimate torch.”

First things first: Where can I find the Mandelkows? Without saying a word, the porter picks up a large map of the complex and, using a thick felt pen, traces the path to the Max Planck Research Unit for Structural Molecular Biology. “A good ten minutes on foot – walking at a brisk pace,” he adds with a grin. The site, which is the size of a small city neighborhood, comprises 80 buildings. Even a young and fit person could easily lose their way here. For someone suffering from dementia, even the best map in the world would be of no use.

Alzheimer’s – the diagnosis always comes as a shock. For the patients themselves, but also for their families. It means a process has begun that can’t be halted: the loss of memory – experience, acquired and everyday knowledge, information about people and things loved and, ultimately, even awareness of the self.

The causes of the disease remain largely a mystery. The consequences are clearly recognizable while the pa-
tient is still alive, but up to now, they really become clear only after death: protein deposits and a conspicuous loss of nerve cells, primarily in the hippocampus, the part of the brain where the memory resides.

Our memory is like a personal library. We can access it whenever we like, select individual books and retreat to particular places and situations, even if they occurred many decades ago. All it takes is a photograph, a smell, a noise, or sometimes just a particular incidence of light, and images that were long believed forgotten trigger chains of thought. **Light like that time in Siena, in the early afternoon. It was September ’94 … I had just bought those tan shoes and we passed this small pasticceria. It smelled amazing! Afterwards, we had those warm almond cookies … what were they called? … that’s right, ricciarelli … and the café…? A day later, the name of the café comes back again: “Café Nannini … .”**

**ALZHEIMER’S CAN AFFECT ANYONE**

But what happens when one book is missing? And then several books? Later, entire years, and even entire epochs, have vanished into thin air. And at some point, all that is left on the empty shelves are dog-eared volumes from childhood and youth. So we read them again and again, almost compulsively. This is more or less how someone who has Alzheimer’s must feel.

An estimated 24 million people throughout the world currently suffer from this most common form of dementia. Fewer than 2 percent of them suffer from familial Alzheimer’s disease. In those patients, certain mutations arise on a chromosome and can be identified using a genetic test. The vast majority of sufferers have sporadic Alzheimer’s disease. The good news is that anyone whose relatives did not display typical Alzheimer’s symptoms from around the age of 50 can feel relatively safe until they are 80. Only three out of one hundred 75-year-olds contract the disease; in 80-year-olds, the corresponding figure is around 20 percent. After 85, it rises to between 30 and 50 percent – depending on the statistics used. “The main risk factor for Alzheimer’s is simply age,” says Eva-Maria Mandelkow. “Just as we develop arthritis in the knee or hip joint, the nervous system is also subject to wear and tear.”

“The astonishing thing is that the majority of us do not get Alzheimer’s in old age,” stresses Eckhard Mandelkow. “All elderly people have protein deposits in their brains. Do they have a protective gene? Good metabolism? We simply don’t know.”
The disease is highly specific. In addition to the loss of neurons, the pathologist will find two kinds of deposits in the brain tissue of Alzheimer's patients: the protein amyloid-beta (Aβ), also referred to as “plaque,” will be observed between the neurons, and tau protein will be found inside the neurons. Only when both occur – and predominantly in the hippocampus – does the patient develop Alzheimer’s. On their own, tau deposits, which are known as tau pathology, are indicative of various other forms of dementia. For example, the presence of tau in combination with the protein alpha-synuclein is a typical feature of Parkinson’s disease. It is also possible to develop both Alzheimer’s and Parkinson’s.

The Mandelkows and their interdisciplinary team have long had tau in their sights. The protein stabilizes the microtubules, the tubular protein fibers that constitute a key component of the basic structure of all cells. They literally play a “supporting” role because they provide mechanical support to the cell. Moreover, during cell division, they form the spindle apparatus, to which the chromosomes in the emerging daughter cells migrate. They also facilitate the cell’s “freight transport” system: valuable supplies access the cell through the cell projections, the axons and dendrites, and are carried “on piggyback” by motor proteins like kinesin, the cell’s very own “freight carrier.” The supplies in question range from proteins and nutrients to entire cell organelles, for example mitochondria and peroxisomes – cone-shaped mini-containers for enzymes.

The entire process can be observed live and in color under the fluorescence microscope, as tau and other cell components can be marked using fluorescent proteins. The image under the microscope resembles slow-moving traffic at the entrance to a tunnel.

**PART OF THE CELL SKELETON**

Tau binds loosely to the microtubules and stabilizes them, helping to ensure that the cellular transport process runs smoothly. This protein is something of an exotic species, as it is almost entirely unfolded. As a result, it is very flexible and can’t be impaired by either heat or acid. “We had already been working on tau and other microtubule proteins for some time when the link between tau and Alzheimer’s was discovered more than 20 years ago. This prompted us to concentrate on the role of tau in this disease,” explains Eva-Maria Mandelkow. In diseased neurons, the protein behaves “improperly” and no longer functions correctly. “In Alzheimer’s, tau is over-phosphorylated by hyperactive enzymes, the protein kinases, such as MARK kinase. This means that phosphate groups suddenly arise at many locations in the tau protein. As a result, it
Mandelkow. The researchers applied the loosely clumped “sick” Aβ protein to rat cells from the hippocampus and observed what happened in the neurons: the first pathological signs of Alzheimer’s emerged with bewildering speed – just two hours later. Tau, which is normally found in the axon, was also found in the dendrites. And wherever the tau arose in the wrong place, the parts of the synapses where signal transmission takes place – the postsynapses or spinous processes – disappeared. This is fatal, as the communication between the nerve cells takes place through the contact of the presynapse on the axon and the postsynapse on the dendrite of the downstream neuron. One neuron has around 10,000 synapses. Even if these points of contact are only partially destroyed, the “radio silence” between the neurons begins.

TAU AND Aβ – THE SEARCH FOR CAUSE AND EFFECT

Eckhard Mandelkow takes a piece of paper and starts to draw. “When Aβ forms clumps, it settles on the postsynapses like a thin film. It is assumed that it binds to a receptor – the NMDA receptor, for example. When it is activated, calcium flows into the cell. That is its job. In this case, however, the NMDA receptor is over-activated, and too much calcium flows into the cell interior. This triggers, among other things, tau dysregulation.”

Does this mean that Aβ is ultimately the trigger of the disease? Mandelkow shakes his head and continues drawing.

Laser scanning microscopes provide particularly detailed images of the brain: Eva-Maria Mandelkow analyzes microscope images of neurons with her husband (top) and Xiaoyu Li (bottom).
That’s not quite the case. It’s always said that Aβ dysregulation leads to tau dysregulation and this, in turn, causes synapse loss and neuronal cell death. But what actually causes the Aβ to clump? Mutations could be one possible cause, but these arise only in the rare cases of familial Alzheimer’s. Many scientists believe that the precursor of Aβ, the cell surface protein APP, is split too often and in the wrong place. And the short Aβ protein that arises as a result has the tendency to form clumps. The gene for APP is on chromosome 21. This is why, for example, people with trisomy 21 (Down Syndrome) have a higher risk of developing dementia early on. An increased amount of Aβ is formed in their brains, as they have three copies of the APP gene.

“By the way, you’ve just drawn the postsynapse incorrectly,” notes Eva-Maria Mandelkow. He smiles. “I don’t like it at all when my wife corrects me...” She laughs and continues. “Well, you did. You drew it as a presynapse. Doesn’t matter, forget it!”

Is it always easy to work together? They glance at each other. “Together we’re actually very creative,” she says. “I do everything by gut feeling.” Eckhard adds: “And I don’t let anyone walk all over me!” They both laugh. They don’t always agree when it comes to the interpretation of their research findings. This is hardly surprising, considering that he is a physicist, and she, a medical doctor.

And, as a doctor, Eva-Maria Mandelkow is interested not only in finding out how Alzheimer’s arises, but also in developing a treatment. The path to this goal leads from cell tests to transgenic mice. These are animals in which a manipulated form of the human tau gene has been transplanted. Some of the rodents received a gene with an anti-aggregation mutation – tau is simply unable to form clumps in them. Others were given the pro-aggregation variant, in which the tau aggregates particularly quickly. These mice develop Alzheimer’s-like symptoms in a matter of a few months. The clever thing is that the gene can be switched on and off again.

**MEMORY TEST FOR MICE**

The scientists have recently been carrying out behavioral tests on the mice. The scenario: The rodents must swim to find their way to a platform in a two-meter-wide water basin. The platform is concealed beneath the surface of a milky fluid. They have already undergone training in finding the platform, four sessions per day. A camera films the mice from above and shows their swimming track as a red line.

And now for the test: First, the healthy mouse, the wild type. Ready, set, go! Within 15 seconds, it paddles to the platform and climbs onto it. Then it’s the turn of the “Alzheimer’s” mice. Their behavior is eerily reminiscent of a person with dementia who is unable to find the way home. One mouse moves through the basin in endless confused circles and even swims right by the platform at one point and then finds it – by accident, because it brushes up against it. The time: 1 minute, 7 seconds – four times longer than the healthy mouse. “This film tells us so much more about the disease than all of the graphs and diagrams,” says Eva Mandelkow, pensively.

Finally, the same mouse, the one that already had “Alzheimer’s” and in which the toxic human pro-aggregation tau had been switched off for 4 weeks, does the test again. The mouse sets off purposefully, turns two quick pirouettes, as if to say, “I’ll be right there!” and, presto, reaches “dry land.” In a mere 10 seconds! “If you examine the neurons in the brains of these mice in detail, you’ll see that they still have tau aggregates and neuronal loss, but the synapses have re-formed!” Eva-Maria Mandelkow’s eyes shine with euphoria.

The brains of these “Alzheimer’s” mice contain clumps of mouse tau and human tau. To the scientist’s amazement, in the animals in which the mutated gene was later switched off, the human tau dissolved again, but the mouse tau remained entangled. Mouse tau doesn’t usually clump together. Strange. It appears it was prompted to do so by the toxic human protein. “That means that mutated – that is, pathogenic – tau can alter healthy tau! Like prions in Creuzfeldt-Jakob disease, but not infectious.” She grins. “My husband doesn’t like it when I say that.” He shakes his head. He sees it differently, from a physical perspective: mutated tau acts more like a crystallization germ that can also cause normal tau to form clumps. The real sensation, how-
ever, is that the memory loss is reversible – at least if intervention comes before too many neurons die off.

A SOLVENT FOR TAU CLUMPS

Switching off a gene – something that works well in mice – is not possible in humans. However, it should be possible to dissolve the tau aggregates using active substances. The Mandelkows’ group has already tested 200,000 substances, identified promising lead structures and chemically refined them with the help of colleagues from other Max Planck institutes and universities. Two of the active substance classes examined have what it takes to dissolve the tau tangles and thus allow the synapses to grow again: derivatives of rhodamine and phenylthiazolyl-hydrazide.

Eckhard Mandelkow pops next door for a minute to consult his computer. His wife explains how they met. “As scholarship recipients of the Evangelisches Studienwerk, a scholarship organization for gifted students funded by the Protestant church of Germany, we were both involved in a performance of the opera Dido and Aeneas.” A voice from next door calls out: “She as a flutist and I as a cembalist.” When Eckhard went to New Orleans on a Fulbright Scholarship, she followed and completed a clinical internship. They both then wrote their doctoral theses at the Max Planck Institute for Medical Research in Heidelberg. This was followed by a period working as postdocs in the US, and the birth of their two children. “My dream was actually to work as a doctor in Africa. But I fell in love with this physicist!” Their daughter, a future surgeon, is now doing just that. She has already spent a year working for Médecins Sans Frontières in the Congo and during the cholera epidemic in Zimbabwe. Their son followed in his father’s footsteps, studying physics and completing his doctorate on magnetic resonance tomography of the brain. He now works in the field of brain research.

The Mandelkows came to Hamburg to the newly established Max Planck laboratory in DESY in 1986 and have worked together ever since. “I focus on the biochemical dimension and the electron microscopy, and my husband does the rest,” says Eva-Maria Mandelkow. As a doctor, structural biology was not quite her cup of tea. But when the tau protein came into play, and with it, Alzheimer’s disease, she was hooked.

Together with colleagues in Munich, Freiburg and Cologne, they are now working on developing other transgenic animal models of Alzheimer’s disease, such as fruit flies, zebra fish and worms. “When the ‘tau worm’ develops the clumping form of tau, it is no longer able to move,” says Mrs. Mandelkow. They would now like to treat the worm using the drugs they recently tested on the mice. “The worm is ideal, of course, as it takes only a few days to go from one generation to the next, and the symptoms of a disease become apparent in a matter of hours.”
With the mice, we have to wait several months until we can observe symptoms.” For the time being, it’s all about providing the “proof of concept.” As soon as the substances are available, the intention is to use them in patients.

ALZHEIMER’S RESEARCH IN BONN AND HAMBURG

Before things get that far, however, the two researchers will be moving to a new city. Next year they are set to transfer to a laboratory in the German Center for Neurodegenerative Diseases (DZNE), which was established in 2009. The DZNE is located on the premises of the “caesar” research institute, an institute of the Max Planck Society. At the DZNE, the Mandelkows intend to research other diseases in which tau plays a role. In addition to an 11.5 Tesla MRI scanner for mice, the scientists will have a host of new possibilities for observing the inside of the brains of live mice in Bonn. “We are really well resourced here in Hamburg – but we don’t have anything like that in our current institute.” However, they would like to keep one part of the laboratory in Hamburg for the time being. “Because of the mice, if nothing else. They can’t simply be moved in the middle of experiments. We work in close cooperation with the University Medical Center Hamburg-Eppendorf and keep more than 1,000 mice there at different stages of aging and treatment.”

Eva-Maria and Eckhard Mandelkow spend between 10 and 12 hours a day at work. This doesn’t leave them much free time. She has to laugh. “The children always used to say ‘our parents have premature Alzheimer’s. They always forget what they promised us.’ That’s what happens when your work and hobby overlap.” Apropos free time: Do you both have other hobbies? “We used to,” he says drily. “My husband plays the piano very well and we are interested in political developments,” she adds. “But our research is so fascinating and we regularly meet our friends at conferences. We occasionally find time to go to the opera. And for relaxation, we go for walks along the banks of the Elbe River.”

As experts, would they want to know whether they had Alzheimer’s – assuming that a test were available with which the first signs of Alzheimer’s-specific protein deposits could be observed at an early stage? She answers without hesitation. “Definitely!”

Is there anything you can do to prevent these protein clumps from forming? “Of course there is. What’s good for your heart is also good for your brain! As long as the brain is well supplied with blood, the supply is right, you’ve done just about everything that can be done at present,” he says. “Lots of exercise, low cholesterol – that’s very important. And then the usual things: vitamins, fruit, fish, reduced calorie intake,” she adds.

Those who have a tendency to develop diabetes also have a much higher risk of developing Alzheimer’s. “The tsunami is on its way, as many children are already too fat! There will be a huge increase in the incidence of diabetes and, for that reason alone, Alzheimer’s as well,” stresses Eckhard Mandelkow. So what about gingko or curcumin? Eva-Maria Mandelkow laughs again. “We don’t believe in that.” Indian and Chinese medicine? “Most of it could probably be thrown out,” he growls.

Despite this worrying prospect, however, the Mandelkows are in good spirits. It’s quite likely that drugs that are able to resolve the Aβ-tau problem will be available on the market in the foreseeable future. And the two scientists will have a well-stocked “library” to consult in their old age, containing shelves filled with memories of their long and shared path through scientific research.

GLOSSARY

Presynapse/postsynapse
The presynapse is the transmitting section of a synapse. This is a specialized region of the axon in which the incoming electrical signal triggers the release of a neurotransmitter. This neurotransmitter binds to receptors in the neighboring postsynapse on a dendrite of the recipient cell and activates further electrical and chemical signal chains there.

Hippocampus
A region of the brain that plays an important role in learning and memory. Its name derives from its curved shape (Latin: seahorse). It is part of the two hemispheres of the cerebrum, so there is also a right and a left hippocampus. Information from various regions of the brain enter the hippocampus and are connected with each other there.

Protein deposits
The proteins consisting of one or more amino acid chains fold during formation into complicated spatial arrangements. Incorrectly folded proteins can combine to form long and short fibers. They not only lose their functionality as a result, but also become insoluble and toxic and can no longer be dismantled by cells.
Electricity Flexes Muscles

Now even paraplegics can ride a bike – thanks to functional electrical stimulation, a method that takes the place of the nerve signals of the brain. At the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg, Thomas Schauer is working on a sophisticated control system for this technology, which also helps get stroke patients quickly back on their feet.

TEXT TIM SCHRÖDER

An electric current gives a strange, tingling sensation when it flows into your skin, as if mineral water were bubbling in your forearm. It is odd to see the flat electrode on your skin and not know how strong those pins and needles will become; but the anticipated prickling stays away. It doesn’t take much electricity to get the muscles moving: first the fingers lift, then the heel of the hand, and finally the whole hand hovers over the tabletop. It falls and rises again with the ebb and swell of the current, apparently of its own accord, rather spookily.

Thomas Schauer is a master of the art of fine-tuned muscular remote control. He gets paraplegics cycling and helps stroke patients learn to walk again. His laboratory contains a huge tricycle for adults, alongside an ergometer with wires trailing out of it. These end in small gray boxes with control dials, and in electrodes for sticking to the skin like band-aids.

Schauer’s specialty is electrical stimulation. He regularly shows his visitors what that is by demonstrating the hovering-hand experiment. Of course, electrical stimulation has been around for a while. As early as the 1960s, scientists tried to help stroke patients walk using small bursts of current. Until quite recently, however, it remained a simple “on/off” technique. Who would have thought that electrical stimulation could be adapted for individual patients, or adjusted for specific situations? Yet this is exactly what Schauer does, using an ingenious computer control unit.

MUSCLES AS COMPONENTS OF TECHNICAL CONTROL LOOPS

The technique developed by the electrical engineer, who specializes in control engineering, doesn’t use muscle stimulation as a blunt instrument. Instead, the computer measures how strongly the muscle responds, how powerfully the leg swings or the foot presses against the floor. Then the system reacts: it adjusts the next electric pulses to the muscle effort to generate a flowing movement. Schauer makes the muscle a component of a technical control loop.
Electronic mobility aids: Patients left with paralysis following a spinal injury or stroke can be helped to perform many movements through functional electrical stimulation. Thomas Schauer, Thomas Brunsch and Jörg Raisch demonstrate the systems that can be used to raise an arm or foot.
Together with his boss, Jörg Raisch, whose control engineering research group is divided between Magdeburg’s Max Planck Institute for Dynamics of Complex Technical Systems and the Technische Universität Berlin, he has made great advances in recent years.

It all began with the idea of teaching paraplegics to ride a bike. At that time, a professor had summoned Schauer to Glasgow University for his doctoral studies, to a new research group focusing on “functional electrical stimulation.” In paraplegics, the conduction of nerve impulses to the muscles is interrupted; the muscles and their corresponding nerves still work, but their connection to the brain is severed. “Back then, we felt that it ought to be possible to generate a harmonious pedaling motion using appropriate control engineering,” recalls the scientist.

Schauer and his colleagues secured the patients’ feet to the pedals using special shoes, and attached electrodes to their legs at the knee flexor, knee extensor and hip extensor muscles. Then they fed data on the position of the pedals into their computer program. It was months before the software was running smoothly enough for all components to work seamlessly together. Finally, it happened.

**A PERFECT BIOLOGICAL STIMULATION SYSTEM**

From a laptop on the carrier rack, the software controlled the electric pulses issued by the small on-board battery and the electrostimulator. Whenever a pedal moved over the highest point on the curve, the electrodes at the knee extensor were activated and the muscle contracted. As soon as the leg was fully stretched, the knee flexor was stimulated and drew the pedal up again. Ultimately, the leg completed a perfect rotational movement. Without any engines to help them, the paraplegic patients were pedaling around on the special tricycle. “It gave people a wonderful sense of freedom to cycle about under their own power,” says Schauer.

Of course, electrical stimulation is a long way from holding its own against natural nerve stimulation. Nerve pathways shoot their microimpulses into individual bundles of muscle fibers with high precision, while the electrodes fixed to the skin are the size of post-its and cause several muscles to twitch at once. Nor are they as accurate as nerve cords at dosing their energy. Consequently, the same muscle fibers are stimulated again and again, and the muscle fatigues quickly.

Schauer wants to improve this situation. In recent years, he has gradually come closer to the perfect biological stimulation system. First, he and his colleagues developed a kind of training ergometer together with medical device manufacturer Hasomed; it has been on the market for about five years now. Paraplegics and stroke patients with paralyzed legs step on the pedals as they sit in a wheelchair. The device includes an electric motor that helps the patients pedal.
In an ongoing project, Schauer is bringing electrical stimulation a step further. This project involves not only the medical device manufacturer, but also neurologists from Berlin’s university hospital Charité. Together, they are working on the details of a kind of intelligent ergometer. The pedals of this device hold force sensors that detect how strongly the leg is pushing, and this enables the software to adapt the strength of the current and intensity of the pulses to the muscle status.

The conventional ergometer had no such control loop; it simply sent pulses to the leg flexors and extensors as a function of the pedals’ position. This meant that the muscle stimulation was always steady – but a muscle doesn’t work like an electric motor. “Muscle effort varies depending on the patient’s condition or even the time of day,” explains Schauer. And then, of course, muscles become fatigued during exercise. The control loop receives data from the force sensors in the pedals, enabling the electrical stimulation to be adjusted so that now, if the muscle becomes fatigued, the device gives a stronger stimulus.

The new ergometer also features electrodes that not only stimulate the muscles, but actually measure their electrical excitation. These are known as electromyographs (EMG), a kind of ECG for muscle function. The EMG gives the control loop additional information about muscle status. This is particularly useful for stroke patients who need to train their legs. Electrical stimulation can support them in this, but using EMG, the system can detect exactly how fit the muscle is, how well it responds to stimulation and how much it contributes to the pedaling movement. A force sensor cannot provide such nuanced information.

And there’s yet another new element. The only adjustments previously possible in electrical stimulation were the strength of the current and the duration of the pulse. This is not enough to simulate natural neuronal excitation, however, because how a muscle works also depends on the rate and frequency of the fine electric impulses. This was too much for the early control devices – Schauer and his colleagues had to resort to screwing and soldering to build the first muscle pulse generator.

**WORKOUT FOR THE CARDIOVASCULAR SYSTEM**

Consequently, they built this technology into the new ergometer, resulting in vastly improved workouts for paraplegic patients. Above all, the legs take longer to fatigue. And then there’s the auxiliary motor that supports beginners as they pedal. For others, the ergometer workout is part of their daily fitness program, and the stronger their muscles become, the less the motor helps them. “Paraplegics have only a limited range of movement, so working with the ergometer is especially important for their cardiovascular system and general condition,” says Schauer.
Electrical stimulation is even more significant for stroke patients as they seek to regain lost skills and overcome paralysis. In a stroke, clots block arteries in the brain, or in other cases, a cerebral artery bursts. Either way, the blood supply is cut off, and without fresh blood and its constant supply of oxygen, definitive tissue death occurs within a short time, resulting in paralysis. “Time is brain,” as medical experts say.

Depending on which area of the brain is affected, various bodily functions previously controlled by that area will fail. A stroke often causes paralysis of the leg, but the brain can compensate for the damage. Healthy areas take over the functions of the damaged part, but only if the brain is taught the movement by repeating it many thousands of times.

Physiotherapists usually do this work – a back-breaking job. Patients are supported by a kind of mountaineering harness suspended from the ceiling as they walk slowly on a treadmill. In time with the steps, the therapist lifts the paralyzed leg and sets the foot back on the treadmill. Weeks of daily training are required before the patient learns how to walk again – and trusts that the paralyzed leg can bear their weight once more.

**STROKE PATIENTS WALK WITHOUT STUMBLING**

Once more, Raisch and Schauer’s control systems have something to offer: As with the ergometer, they lift the knee, tilt the foot, and put it down again. Thanks to appropriate electrical stimulation, the muscles themselves do what therapists have usually done to date. It doesn’t sound much more difficult than stimulated cycling, but a step is a fast thing. Depending on the pace, it might take only a second. The control system has to keep up and even work faster, because the muscle reacts to each pulse with a time delay. As a result, Schauer’s path to achieving fluid movement was a long one. He and his colleagues spent several years programming and optimizing. A prototype of the control software is now being used in treadmill training at a clinical center.

With experience, Schauer’s expectations of his electrical stimulation programs grew: first, the experiments with the tricycle and the ergometer, which guide and hold the patient securely as the pedals are turned; then walking on the treadmill while suspended; and finally, even more complexity – independent walking without stumbling. About one in five stroke patients who learn to walk again end up with “foot drop,” a disorder in which the brain does not fully activate the dorsal flexor of the foot, that is, the muscle that lifts the toes when the foot swings forward. Initially, the dangling toes make patients stumble, but in time, they learn to use an evasive movement, swinging the foot out to the side in a semicircle. This unsteady gait prevents stumbling, but is rather tiring. Climbing stairs becomes an arduous challenge.
For a number of years now, electrostimulatory walking aids have been used for foot drop. Patients wear shoes with pressure sensors. When they lift a foot off the ground, the sensor in the sole of the shoe sends a command to the stimulator, which emits such a strong current that the foot is lifted way up high – a safety measure to ensure that nobody stumbles. Unfortunately, this causes rapid fatiguing of the muscle. These conventional systems offer only simple on-off functionality; they have no way of adapting to the muscle condition or effort of the patient’s leg. Once again, the control loop provides a solution.

How, then, to fix foot drop with correct positioning and without overfatiguing the muscle? In order to walk safely, the foot must land, roll and lift perfectly, with a precision of fractions of a second. One of Raisch’s doctoral students at the Magdeburg-based institute had an inspired idea: it should be possible to control such a system accurately if the exact position of the foot is known – preferably using a sensor on the shoe itself. He worked meticulously on this idea for the full course of his doctoral studies, and finally came up with a small sensor that could be clipped onto a shoe. This fast-acting gadget takes mere milliseconds to calculate the height, acceleration, position and angle of the foot.

Speedy calculation of the position is not enough, however, because the muscles need to be stimulated just as quickly. A zippy control system was also required. “It quickly became clear that the whole system is too slow if we want to calculate the position while the foot swings forward and adjust the intensity of the stimulation at the same time,” says Schauer. A muscle is simply too sluggish. Before it reacts to an electric pulse, the foot is already back on the ground.

Instead, the software analyzes the data after each individual step in a matter of milliseconds, and has a suitable stimulation pattern ready before the next step is taken. This means that the system constantly learns from past steps and adapts the pulses for each subsequent step. “Iterative learning” is Raisch’s term for this strategy, which makes flexible correction of foot drop possible for the first time.

First, though, the team of scientists had yet another hurdle to overcome. Every sensor, every technical system, makes tiny mistakes and therefore, in the course of time, deviates from the ideal or target value. A wristwatch, for instance, may be several minutes slow after some weeks. If these errors accumulate, the situation becomes critical. It’s
no big deal with a wristwatch – we just reset it; but a position sensor that deviates significantly from the correct position after 50 steps is dangerous, as it will cause patients to stumble. Consequently, the electrical engineers designed the software in such a way that it constantly self-calibrates and errors do not accumulate.

For now, the sensor is too expensive for general use in the daily lives of stroke patients, and too big – although it is only the size of a matchbox. Besides, the sensor, stimulator and controls interact only by means of a complex wiring system, which can be rather troublesome in daily life. A wireless solution would be better.

As a result, Schauer and his team have been working for some time on another, rather unusual position sensor: a bioimpedance sensor. This measures the electrical resistance between several points on the lower leg. What is really fascinating is that, as the leg moves, and particularly as the skin and muscles stretch, the electrical resistance (or bioimpedance) changes. Ultimately, this means that a control system could deduce the position of the foot and activate the dorsal flexor with a perfect fit.

**THE GOAL: SOCKS WITH INTEGRATED ELECTRONICS**

Schauer’s bioimpedance work is still in its infancy, but the procedure seems promising, given that it is a low-fuss system. However, it can’t quite yet manage without wires because the electrodes on the lower leg need to be connected to the control electronics. Still, Schauer has thought up a solution for this, too: one day, patients will wear stockings with integrated electrodes and contacts. Unfortunately, the sensor electronics currently used to determine the position of the foot could hardly be knit into a sock.

Schauer’s newest project, which he is working on with doctors from Berlin’s trauma center (Unfallkrankenhaus Berlin – UKB), is also based on bioimpedance measurements and focuses on the treatment of swallowing disorders. Just as the death of brain tissue following a stroke often causes paralysis of the leg muscles, it can also affect the muscles that control swallowing. In such cases, the windpipe is no longer fully closed during the swallow re-
Food and drink slip into the lungs, leading to severe inflammation. Often the only solution is a tracheotomy or tube feeding, where the care assistant injects the food into the stomach through a tube.

MEDICAL INNOVATION AWARD FOR SWALLOWING AID

If it were possible to control the larynx area in the same way as a paralyzed leg, it would mean that the swallowing muscles could be suitably activated and the windpipe protected. The system would monitor the muscles using bioimpedance measurements and assess whether food is moving toward the esophagus or accidentally ending up in the windpipe.

The concept of detecting choking by means of external measurements seemed rather absurd initially, even to Schauer and his medical colleague, Rainer Seidl of UKB. So they brought a cow’s throat into the laboratory and inserted wafer-thin needle electrodes into the tissue. “We really had no idea whether or to what extent changes in resistance could be measured from the outside when fluids flowed through the larynx.”

The first attempts were promising, so Schauer and his colleagues ultimately attached electrodes to their own necks. “Now we really can use the resistance values to draw conclusions about muscle activity and the swallowing process.” A short time ago, Germany’s Federal Ministry of Research awarded Schauer and Seidl the Prize for Innovation in Medical Technology. This financial injection is helping them drive the project forward. Their goal is to create a high-tech implant that few people have ever heard of. Prosthetic arms and legs are nothing new, but if all goes well, Raisch, Schauer and Seidl will achieve something quite different: an electronic swallowing prosthesis to get the larynx moving.

GLOSSARY

Functional electrical stimulation
This method is used when the areas of the brain responsible for muscle control are damaged and can’t emit signals along the nerves. External currents are used to stimulate the nerves and make the muscles contract.

Electromyography
provides information on the electrical activity of a muscle. It measures both the spontaneous activity of the muscle at rest and the action potentials of the contracted muscle.

Bioimpedance
A measure of the body’s resistance when an external current is applied.
First the Trial, Then the Moralizing

When is it legitimate for laws to cite ethical standards? This issue is the focus of an Independent Research Group headed by Silja Vöneky at the Max Planck Institute for Comparative Public Law and International Law in Heidelberg. Doctoral student Mira Chang is investigating the circumstances under which international drug trials may be unlawful.

TEXT HUBERT BEYERLE

In the movies, it’s very simple: there are the good guys and there are the bad guys. In the recent film version of John le Carré’s novel The Constant Gardener, the bad guys were the guys from the unscrupulous drug companies who tested their new products in Africa and were willing to accept a few deaths along the way. In an afterword, the author fulminates that “by comparison with the reality, my story [is] as tame as a holiday postcard.”

In novels as in films, the world is allowed to be black and white. The reality, however, is somewhat more complex. Just how complex is revealed only through systematic research. But how do you research good and bad or right and wrong in the context of verifiable science?

The scandalous aspect of medical progress is not new: it lies in the divergence between those who provide innovation and those who benefit from it, since advances in medicine – as in every other branch of science – are made by trial and error. The only difference is that, in medicine, errors can be fatal. Theory goes a long way, but not quite far enough. And sooner or later, in the development of new drugs, there comes a time when the animal experiments have all been conducted and the substance must be tested for the first time on a human subject. He or she becomes part of the experiment: the means and not the end.

PHARMA INDUSTRY FOCUSES ON POOR COUNTRIES

The globalization of pharmaceutical research has further intensified this moral conflict: more and more drugs are being tested in poor countries. In the past 15 years, the focus of drug research has gradually shifted to Latin America, Asia, Eastern Europe and Africa. China and India in particular are the new hotspots in what has since become a multi-billion euro market.

There are two main reasons for this: supply and demand. On the one hand, trials are expensive. It can take ten years or more before a new drug is approved for use. The cost of bringing a product to market can run into the hundreds of millions, even to a billion euros. The figures are disputed, but this much is certain: trials are expensive. That is why it is worth conducting them in poor countries.

But it isn’t just money that motivates drug companies to internationalize their research: fewer and fewer people in the rich countries of Europe and North America are willing to act as guinea pigs. Some studies indicate that more than half of the trials conducted worldwide are now taking place outside of the established US, EU and Japanese markets. This globalization of drug research brings with it a plethora of moral issues. The pharmaceutical companies and their service providers, the contract research organizations, have
recognized this fact and consistently emphasize their observance of “ethical standards.”

Indeed, there has long been an abundance of international codes, conventions and standards of good practice. Regulatory authorities, the drug companies themselves and physicians have laid down international rules that at least sound good. They have even established ethical committees to oversee compliance with the rules. Basically, it is always about expressing commitment to “ethical principles.” Does that mean the problems are solved?

“No,” says Mira Chang. As a doctoral student at the Max Planck Institute for Comparative Public Law and International Law in Heidelberg, she is highly critical of these frequent references to ethical standards. “Ethical standards are all well and good, but it’s more than just a matter of ethics. There are some central legal issues to be considered, as drug trials can in-

Ethics and science in conflict: Pharmaceutical companies are testing more and more drugs in poor countries. The result is a potential moral time bomb.
“fringe on human rights,” she says. “There are international declarations and guidelines that define ethical standards, but when these emanate from private institutions, their legitimacy may be questioned.”

NO CLAIM TO REPRESENT ALL DOCTORS

The most important declaration, the Ethical Principles for Medical Research Involving Human Subjects, was adopted by the World Medical Association (WMA) in Helsinki in June 1964 and most recently amended in 2008. This document specifically states that the welfare of the patient must take precedence over the interests of science and society. In addition, particular consideration should be given to the special needs of economically and medically disadvantaged persons.

That sounds good. Isn’t that all there is to it? “No, most certainly not,” says Mira Chang. In fact, for the legal experts, this is where the work starts. “This declaration is not a legal document,” Mira Chang continues. “It was adopted by a body of experts whose legitimacy is open to question. This body is dominated by European and North American medical associations. It cannot claim to represent all physicians. And third parties, such as the test subjects, have no say at all.” What’s more, membership and voting rights are dependent on payment of a membership fee. Mira Chang is critical: “This is a rather unconvincing basis for a body whose ethical principles are supposed to apply worldwide.”

In its purest form, the whole moral dilemma surrounding medical research is reflected in the placebo problem. Scientists and regulatory authorities largely agree that placebo tests are necessary in order to be reasonably certain, firstly, that a drug is safe, and secondly, that it works. Ideally, such tests are conducted as a double blind study with neither patient nor doctor knowing which pill is which. However, doctors are under a professional obligation to administer the best medicine available. So how can they intentionally withhold a supposedly effective medication from some of their patients?

The dilemma lies in the fact that, on the one hand, those who receive the medication are being used as guinea pigs with no real certainty as to the effect, while those who receive the placebo are denied the medication that might well benefit them. Both aspects are ethically problematic. In Mira Chang’s view, there is only one solution: “If another proven drug already exists, in the case of life-threatening conditions, placebo tests cannot be justified.”

RESEARCH AT THE FRONTIER BETWEEN ETHICS AND LAW

Science cannot ultimately determine what is morally right or wrong. “Morality as an empirical phenomenon may be the subject of scientific study, but there are many moral problems to which ethics cannot provide a single, unquestionably correct answer,” says Silja Vöneky, a professor at the Albert Ludwige University of Freiburg and head of the Independent Research Group at the Max Planck Institute in Heidelberg. There is, however, one key difference between morality and ethics. “Ethics, as a reflective discipline, is a normative branch of science. It addresses the questions: How may we act? What are we allowed to do? Ethics considers whether an answer to these questions is inherently consistent or contradictory,” she explains.

Silja Vöneky works at the frontier between ethics and law, the so-called ethicalization of law. She and her research group are investigating where and how extra-legal ethical rules have found and find their way into legal systems worldwide, and how references to ethical standards can be legitimized. It seems self-evident that the provisions of the law should not contradict ethical principles or moral intuition.
Nevertheless, there is a problem, as there is an increasing tendency for laws to include explicit references to ethical principles, and to grant decision-making authority to so-called ethics committees. Who can say that these committees are genuinely competent? In any case, there is justified room for doubt as to whether physicians alone are the right experts to rule on ethical issues with regard to questions of research on human beings,” says Silja Vöneky.

Ethics codes and ethics committees are a relatively new phenomenon. Until a few decades ago, the field of medical research – in practice, at least – seems to have been virtually untouched by ethics or by law. The general belief in progress held sway into the 1960s.

When physician and scientist Jonas Salk wanted to test his polio vaccine against an inert placebo in the US in 1954, the local health authorities refused to take part.

The bone of contention was not, however, the new vaccine, but the inert placebo. So great was their faith in research that the authorities did not consider it acceptable to deny children the new and untested vaccination. When the results of the trials were published, the event attracted national attention. Even the church bells were rung.

This optimism was shattered rather abruptly by the thalidomide tragedy. Between 1957 and 1961, thousands of pregnant women worldwide were prescribed an antinauseant containing the active ingredient thalidomide. The drug had barely been tested, since there were few if any regulations that required it. In Germany alone, some 5,000 children were born with severe birth defects.

Drug trials ultimately require human subjects

One of the consequences was a clear change in the attitude of experts and the public at large toward medical research. Worldwide, development of reg...
The legal studies undertaken by Mira Chang are aimed not just at forming an ethical appraisal of the issue of global drug trials, but at getting a firm legal grip on it.

For years, these principles were known, but barely heeded. Prior to the 1970s, few if any regulations gave legal force to these ethical principles. It took the thalidomide tragedy and the equally infamous Tuskegee experiment in the US to finally engender an increasing awareness in the 1960s and 1970s that the pharmaceutical market had to be regulated.

In the Tuskegee study from 1932 onward, hundreds of black Americans suffering from syphilis were denied the antibiotics that were already available at the time in order to observe the natural course of the disease. It was not until the 1970s that reports of the study appeared in the newspapers, prompting a nationwide outcry. The experiment was terminated after about 40 years. Presidents Bill Clinton and Barack Obama both apologized for the human experimentation that was carried out over decades.

The legal studies undertaken by Mira Chang are aimed not just at forming an ethical appraisal of the issue of global drug trials, but at getting a firm legal grip on it. This is no easy task, given that legal systems are still essentially national by nature, as sovereignty ultimately lies with the nations themselves. But who has jurisdiction when a US company tests its drugs in Africa?

This is a matter of international law – a legal discipline that still attracts suspicions of idealism, particularly since, in recent years, individual human rights have consistently gained in significance at the expense of collective national sovereignty, as evidenced by the debate about the legitimacy of military deployments in the Balkans, Afghanistan and Iraq.

"There are currently some interesting developments in the field of international law. Human rights are gaining in importance and companies are, to some extent, acquiring legal personality. This could be very significant for the debate about drug trials," says Mira Chang. But there is still a long way to go – and so far, the patients concerned have seen little benefit. “Because this still doesn’t result in many obligations for companies.” But that could change. Sooner or later, citizens of an African country may be able to bring legal action against Europe or the US for breach of their human rights if the conditions of a trial clearly do not meet certain minimum standards.

THOSE WHO DO NOT HELP ARE JUST AS GUILTY

In fact, this is not such a utopian vision: it is already happening, thanks to an unusual law in the US that permits such claims. The company Pfizer recently felt the effects. During an epidemic of meningitis in Nigeria in 1996, Pfizer tested a new antibiotic against an established drug. Eleven children died, five of whom had received the new drug Trovan, while six had been treated with the proven Ceftriaxon – but, according to the written judgment, in a dosage that was known to be too low.

The case is a prime example of the moral failings of pharmaceutical companies. Nevertheless, Trovan subsequently received partial approval in the US. Last year, the competent US court admitted the claim against Pfizer. But that is not really a solution to the problem. This much is certain: those who do not render assistance despite being able and obliged to do so are guilty of immoral conduct and liable to punishment. But who does that apply to? In the case of a road accident, it clearly applies to those who were at the scene but failed to help. But who is "at the scene" of the AIDS epidemic in Africa?
Mira Chang proposes that, in the case of drug trials, the buck should stop with the pharmaceutical company conducting the trial. Conducting a trial conveys an obligation. What’s more, the party conducting the trial should be responsible for other things as well, such as proper follow-up care for the patient. That, too, is not a matter of course.

The drug companies’ arguments would then collapse. They regularly emphasize in their defense that “We didn’t have to conduct the trial. If we hadn’t, those concerned would be worse off, with no treatment at all.” It is indeed true that the health systems in many countries of the world are so poor that taking part in a trial is the only treatment option available. But does this “what if we hadn’t?” have any role to play? “It cannot be a corollary of the differences between healthcare systems that these people should be treated differently under the law,” says Mira Chang.

What does the future hold? Actually, even today’s imperfect legal system offers some scope for improvement. “I think we can make a start with the approval procedures,” believes the Max Planck doctoral student. EU law requires that overseas studies be accompanied by a statement that they meet the ethical requirements of the EU Directive on Good Clinical Practice. This Directive, in turn, refers to the Helsinki declaration mentioned above. “The terms are very vague,” says Mira Chang. “They need to be better structured with legally binding effect.”

**MEDICAL RESEARCH IS THE MAIN BENEFICIARY OF STANDARDS**

One concrete legal consequence might be that trials will be approved only if it is intended to subsequently make the drug available in the country where the trial is conducted. Breach of this undertaking could at least attract retrospective sanctions. “To me, it seems that there should be an ethical obligation to allow the population in the country where the trial is conducted to share in the potential benefits, primarily by distributing the drug there once it is approved. This could also be legally framed,” says Mira Chang.

There have already been some improvements in recent years. Many countries, China among them, have established ethical and legal standards of protection that, at first sight, appear to be as good as those in Europe or the US. “But only prima facie,” Mira Chang
continues. On closer examination, it is evident that medical research is the main beneficiary of these standards. They are aimed at raising data quality and the subsequent likelihood of approval. They are only partly intended to protect patients. Also, there is little evidence of whether the standards are adhered to in practice.

As a result, legal research needs to take an approach that is as visionary as it is down to earth and pragmatic. There is much to be wished for, but what is realistic? And what does realistic mean? For law experts, realistic means the ability to develop and derive a compelling position from generally recognized material, such as the Declaration of Human Rights.

In this situation, a unique feature of the law is revealed that makes the work so difficult, but at the same time so interesting. The law is man-made, but it also has a life of its own and is not entirely controllable. It continues to develop in the context of its cultural environment. What was normal 50 years ago is impossible today, and vice versa. Above all, legal norms today are far more explicitly dependent on ethical norms than was once the case.

**THE DIFFERENCES ARE GROUNDED IN CULTURE**

Today, it is held as self-evident that a legally satisfactory solution must also ultimately be morally convincing. Nevertheless, moral intuition may be important, but it is not everything. “Counter-intuitive solutions are permissible, but they require far more justification,” says Silja Vöneky.

In recent times, ethical conventions, codes, and ethics committees have acquired increasing importance everywhere, not just in medicine. While there is common ground as far as general principles in essential issues are concerned, when it comes to details, there are substantial culturally grounded differences. For instance, between a utilitarian viewpoint, which attaches a relatively high value to science and society.
scientic progress, and a deontological perspective, which attaches sigfi-
cance to ethical standards per se and tends to favor the protection of the
individual – such as expressed by the
categorical imperative that no person
shall be exclusively the instrument
of another.

Asian value systems have yet other
ephases. The drug trial issue cuts
right across this: on the one hand, there
is the benefit to mankind; and on the
other, the right of the individual to
physical inviolability. Which ethical
principle is correct? There is no defini-
tive answer. “That is why ethics com-
mitees cannot have the last word,”
says Mira Chang.

**GLOSSARY**

**Deontology**
Deontology refers to a class of ethical theo-
ries that define certain actions as intrinsi-
cally good or bad. There are various shades
of deontological ethics. While moderate
deontologists also admit the moral relevance
of the consequences of an action, moral
absolutism proscribes certain actions under
any circumstances, regardless of their
consequences.

**Ethics**
A major branch of philosophy, dealing with
morals and, in particular, their justification.
Ethics is the study of human actions and is
the starting point for various disciplines such
as legal, political and social philosophy.

**Utilitarianism**
Utilitarianism bases the ethical
evaluation of an action on the
principle of utility, applying the max-
im: “Act in a manner that promotes
the greatest good.”

**World Medical Association**
The WMA is a confederation of
ational medical associations. It was
founded in 1947 and represents almost
100 national professional bodies.
The WMA endeavors to promote high
ethical standards of healthcare and
provide physicians with ethical
guidance in the form of declarations
and position papers.

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Do Chimpanzees Grieve for their Dead Children?

Ape mothers find it difficult to let go of their dead infants

Grief is a deeply human emotion. But what do animals feel when they are confronted with dead members of their species? Chimpanzees are apparently very bewildered and disturbed. Film captured by researchers from the Max Planck Institute for Psycholinguistics in Nijmegen (The Netherlands) seems to substantiate this interpretation. The moving scenes show how the chimpanzee Masya laid her infant, which had died two days previously, on the ground in a clearing. For an hour afterward, she repeatedly approached the corpse and touched it. Then she carried it to a group of other chimpanzees and watched as they inspected the lifeless body. She remained with the infant until the following day. Whether chimpanzees actually feel grief cannot objectively be judged on the basis of these images. However, the observer is a witness to a transitional phase in which the mother learns to fathom the death of her child. (American Journal of Primatology, January 21, 2011, published online)

www.youtube.com/user/MaxPlanckSociety#p/c/5/jzrigeznnqw

A chimpanzee mother with a young animal.

A Quantum Writer for Single Atoms

The spin of individual atoms in an optical crystal can be deliberately modified so that they can be used as quantum bits

It is now possible to write data in individual atoms. Physicists from the Max Planck Institute for Quantum Optics and the Ludwig Maximilian University of Munich have skillfully manipulated individual spins in a quantum gas made up of rubidium particles. Expressed in simple terms, the spin is the rotational direction of an atom. Researchers working with Stefan Kuhr and Immanuel Bloch used a microscope developed specifically for the purpose to address each individual particle in a collection of atoms that lie in overlapping laser waves, as if in an optical egg carton. The experiment achieves a prerequisite for processing information with atoms in an artificial light crystal, as has been proposed for a quantum computer. Above all, however, the work has opened up completely new ways in which researchers can investigate quantum processes. For example, in the course of this study, they observed for the first time how individual massive particles, namely rubidium atoms, tunnel through potential walls. (Nature, March 17, 2011)
Dangerous Oxygen

Long-lived reactive intermediate forms of oxygen that form on aerosol particles could be the reason why allergies are on the rise.

Thanks to new findings by researchers from the Max Planck Institute for Chemistry and the Paul Scherrer Institute in Switzerland, it has now become clearer how toxic and allergenic substances are formed in the air we breathe. Scientists working with Ulrich Pöschl have, for the first time, shown that there are long-lived reactive intermediate forms of oxygen on aerosol particles, such as soot and pollen. The oxygen forms are created when the particles react with ozone. They survive on the particles' surface for more than 100 seconds and, in this time, combine with other air pollutants, such as nitrous oxides. In chemical terms, the particles are oxidized and nitrated. This is what makes the soot particles more toxic and increases the potential of pollen to trigger allergies. As industrial and vehicle exhaust gases have increased the atmosphere's ozone content over the past few decades, this process could explain why the incidence of allergies has increased in recent years. (Nature Chemistry, February 20, 2011)

As Alike as Cat and Dog

Embryonic development reflects evolution

Embryos of different animal species are astonishingly alike. Researchers at the Max Planck Institute for Molecular Genetics in Dresden and at the Max Planck Institute for Evolutionary Biology in Plön have now shown in two studies that the oldest genes in phylogenetic terms are active during the phase when the similarity is at its greatest. Before and after the “phylotypical” period, in contrast, the species-specific genes dominate. Gene expression during embryonic development is thus similar to an hourglass with the phylotypical period as the indented section. The species of a phylum become more similar outwardly and genetically toward this point, and then become more different again. The studies show that, generally speaking, 19th century naturalists such as Charles Darwin and Ernst Haeckel were correct with their hypothesis that embryonic development mirrors phylogeny. (Nature, December 9, 2010)

The Rights and Wrongs of Right and Left

When people are no longer able to move their dominant hand smoothly, their moral judgment changes

A glove can change someone’s attitude. Daniel Casasanto at the Max Planck Institute for Psycholinguistics in Nijmegen in the Netherlands and Evangelia Chrysikou from the University of Pennsylvania asked naturally right- and left-handed individuals to set out domino tiles with their dominant hand in a clumsy glove to which, furthermore, the second glove was loosely attached. After just a few minutes, the subjects no longer associated this side with the “good side.” The researchers also observed this situation in those people who can no longer move their dominant hand smoothly after a brain injury. Normally, right-handed people consider the right side to be good, and left-handed people consider the left side to be good (see MaxPlanckResearch 4/2010, p. 44). For example, out of two applicants, they will unconsciously prefer the one whose photo is on the relevant side. This current study confirms that people associate positive things with their preferred hand, as they can move it more easily. (Psychological Science, March 9, 2011)
The Engine that Powers Short Gamma Rays

A simulation of colliding neutron stars explains cosmic bursts of radiation

They’ve puzzled scientists for years: short bursts of gamma rays that release more energy within fractions of a second than our galaxy, with its 200 billion stars, does in 12 months. What’s behind these outbursts? Researchers working with Luciano Rezzolla at the Max Planck Institute for Gravitational Physics have come one step closer to finding a solution. Using the institute’s Damiana supercomputer and a set of calculations lasting six weeks, they simulated the merging of two neutron stars to form a rapidly rotating black hole. This was initially surrounded by a ring of hot matter with a relatively weak and chaotic magnetic field. The rotation of this unstable system induced an extremely powerful and perpendicular magnetic field of 10 supercript 15 Gauss along the rotational axis, creating in turn a jet of ultra-heated matter that shot across space in two bundles of rays and briefly flared up in the gamma ray range. The researchers allowed the simulation to run twice as long as normal. (The Astrophysical Journal Letters, April 7, 2011)

Two neutron stars merge within milliseconds to form a black hole. A strong magnetic field is generated along the rotational axis and creates a jet that hurls ultra-hot matter into space. Flashes of gamma light can occur in this jet.

Nanosensor Sniffs Out Pathogens

Using tiny nanotubes on a chip, it is possible to detect even the smallest traces of genetic material quickly and reliably.

Researchers from the Max Planck Institute for Solid State Research in Stuttgart used sensors made of carbon nanotubes to detect tiny traces of DNA. Because the sensors respond to specific DNA sequences, they can be used to detect virus or microbe infections in blood samples. The nanosensors created by the scientists working with Kannan Balasubramanian are so sensitive that it is no longer necessary to concentrate or tag the DNA in a time-consuming process, which has been the case up to now. This means that they may be able to deliver diagnoses faster than traditional methods. Furthermore, the researchers have already developed a routine method for manufacturing their nanosensors that makes rapid mass production possible. The end product could be a cell-phone-sized analysis device that can be used anywhere. (Angewandte Chemie int. ed., March 18, 2011)

DNA testing with a nanotube: Single strands of the DNA that is being tested are attached to the carbon nanotube’s surface. The matching DNA pieces (yellow) from the specimen settle on them and change the nanotube’s conductivity.
Dark Matter not a Growth Factor

Galaxy bulges determine the mass of central black holes

At the center of most galaxies is a massive black hole. The heaviest are found in the largest galaxies, which, in turn, are surrounded by pronounced halos of dark matter. Scientists thus suspect that there could be a direct association between dark matter and black holes. A study by researchers from the Max Planck Institute for Extraterrestrial Physics, the University Observatory Munich and the University of Texas in Austin contradicts this view: it is the bulge, the dense central area of a galactic system, that determines the mass of the central black hole. The team examined galaxies that are embedded in massive halos of dark matter and therefore rotate at high speed, but have no or only small bulges. Their investigations showed that galaxies without a bulge contained – at best – black holes with very low mass, even if they were surrounded by massive halos. Therefore, it seems plausible that a black hole is fed by the bulge and thus grows. (NATURE, JANUARY 20, 2011)

Mussel Plastic

A polymer created in a laboratory has similar properties to a mussel protein, because it is cross-linked in the same way

Materials scientists like to be inspired by mussels: they copy mother-of-pearl, the adhesive that attaches the crustacean to the ground, the byssal fibers of their feet, and now the particularly tensile, strong and self-healing protein that surrounds the byssus as well. Scientists in the US have synthesized a polymer with similar structural properties to that which scientists working with Matt Harrington at the Max Planck Institute of Colloids and Interfaces discovered earlier.

Both the mussel protein and the artificial material are crosslinked with iron atoms, from which they derive their special properties. Synthetic polymers based on mussel protein could be suitable for use as new adhesives in underwater technology and in medicine. (PNAS EARLY EDITION, JANUARY 28, 2011)

I Spy with my Little Eye Something ... Green

Thyroid hormones regulate visual pigments in the eye throughout life

The thyroid gland uses hormones to determine how mice and rats see color. Thyroid hormones suppress the creation of UV/blue pigment in the color-sensitive cells in the retina and activate the production of green pigment. According to scientists at the Max Planck Institute for Brain Research in Frankfurt am Main, this is a lifelong effect. If the thyroid regulates the visual pigments in humans in a similar way, a low level of hormones caused by insufficient iodine in the diet or removal of the thyroid would affect the pigments in the cones and cause problems with color vision. As thyroid deficiency is usually treated before it can cause changes to vision, these dysfunctions have not been noticed before now. (JOURNAL OF NEUROSCIENCE, MARCH 30, 2011)
Hope for Arctic Sea Ice

According to new calculations, it is still possible to stop the retreat of the summer ice in the Arctic.

The retreat of the summer ice that has been observed in the Arctic for some years could be halted. The rapid disappearance of the summer ice had given rise to concerns that the ice sheet might be close to a tipping point, as seawater absorbs substantially more heat without a cover of ice. Were it to go beyond the tipping point, the loss of the remaining sea ice would be unstoppable. However, the current results of research by a team working with Dirk Notz at the Max Planck Institute for Meteorology in Hamburg now indicate that there is no tipping point of this kind for the loss of summer ice in the Arctic. Instead, the ice cover reacts quite directly to the prevailing climate conditions. The progressive loss of the Arctic sea ice could thus be slowed down or even stopped – but only if there were a halt to global warming.  

(Geophysical Research Letters, January 26, 2011)

A Breakthrough in Scar Tissue

Cancer drug helps regeneration after spinal cord injury

When nerve bundles in the spinal cord are crushed or severed, the result is usually incurable paraplegia. Scientists at the Max Planck Institute for Neurobiology in Martinsried have made nerve cells in the spinal cord regrow with the cancer drug Taxol. The substance stabilizes the microtubuli, tube-shaped molecules in the cell skeleton, so that the axon of a damaged nerve cell can regenerate. Furthermore, Taxol prevents the formation of an inhibitor in the scar tissue. Rats with newly damaged nerve cells in their spinal cord can walk considerably better after a few weeks, thanks to Taxol. The scientists next want to examine whether Taxol is still effective when the injury lies some time in the past. The side effects and interaction of Taxol with other drugs are well known, which makes clinical development much easier. It is, however, still unclear whether the substance will have the same effect on human nerve cells as on those of rodents. (Science, January 27, 2011, published online)
Italian for Beginners

Babies recognize the rules of grammar in a foreign language earlier than previously thought

“Il fratello sta cantare” – the brother is sing. German babies as young as four months old hear that there is something wrong with this Italian sentence. When researchers from the Max Planck Institute for Human Cognitive and Brain Sciences played the correct and then the incorrect Italian sentences to the babies, they registered the differences after learning for just a quarter of an hour. At this age, content errors are not recognized, but babies recognize and generalize regularities in the sound sequences long before they have any understanding of the meaning. Interestingly, small children learn a foreign language in a completely different way than adults:

(PloS ONE, March 22, 2011)

A New Phylum in the Animal Kingdom

They are tiny, with a mouth that is simultaneously an anus. And instead of a brain, they have a diffuse nervous system. Nevertheless, Xenoturbella and the so-called acoelomorph worms, both groups of simple marine worms, are more closely related to humans than, for example, the common earthworm. An international team of scientists including Albert Poustka from the Max Planck Institute for Molecular Genetics in Berlin discovered that both groups are more closely related to complex organisms from the Deuterostomia (“new mouth”) line than previously thought. In the Deuterostomia, the original mouth from the beginning of the embryonic development becomes the anus, and the mouth develops later. Previously, three deuterostome phyla were known: the chordates (e.g. vertebrates), the echinoderms (sea urchins, starfish, sea cucumbers) and acorn worms. Xenoturbella and the acoelomorph worms together now form the fourth phylum. These “Xenacoelomorpha” were not always as simply structured as they are today. The worms have simplified their construction plan, as that was clearly as advantageous or even more advantageous than a complicated body structure. (NATURE, February 10, 2011)

A Giant Star with a Thick Dust Disc

New 3D imaging technology reveals an invisible companion

A supergiant stands on the brink of death – yet it behaves like an infant. The old star is surrounded by a dust disc that one would otherwise expect to see only with a newborn. The strong particle wind that the bright sun HD 62623 blows into space would destroy a dust disc. A team working with Florentin Millour from the Observatoire de la Côte d’Azur and Anthony Meilland from the Max Planck Institute for Radioastronomy has made a detailed three-dimensional image of this star and its immediate surroundings. It not only shows the structure of the material within the dust disc, but also its movement. It is likely that a close companion star is acting as a source by feeding the disc with its material. Because it is more than a thousand times less bright than HD 62623, the small partner remains invisible; its existence is revealed by a gap in the material between the disc and the central giant star. (ASTRONOMY & ASTROPHYSICS, JANUARY 26, 2011)
An ice-cold experiment: The samples researchers at the Max Planck Institute for Chemical Physics of Solids are investigating are cooled in this dilution fridge to below minus 273 degrees Celsius. This is done by carefully lowering the instrument into a well-insulated cryostat.
Superconductivity Is Pair Work

Electric cables that routinely conduct electricity without loss – physicists have been motivated by this idea ever since superconductivity was discovered 100 years ago. Researchers working with Bernhard Keimer at the Max Planck Institute for Solid State Research in Stuttgart and Frank Steglich at the Max Planck Institute for Chemical Physics of Solids in Dresden want to gain a detailed understanding of how unconventional superconductors lose their resistivity.

April 8, 1911. At the University of Leiden in the Netherlands, two men sit in a darkened booth. Only their instruments tell them what is happening in the cryostat next door. A man in his late fifties with a striking walrus mustache fiddles with this enormous thermos flask: Heike Kamerlingh Onnes has been famous ever since he became the first person to succeed in liquefying helium in 1908. This enabled him to reach the extremely low temperature of 4.2 Kelvin, which is around 4 degrees above absolute zero, at minus 273.2 degrees Celsius. For this achievement, Kamerlingh Onnes would be awarded the Nobel Prize for Physics in 1913.

The cryostat now contains a small glass tube filled with mercury. The Leiden-based physicists want to use it to observe, for the first time, how the electrical resistivity of metals behaves when the temperature approaches absolute zero. At 4.2 Kelvin, minus 269 degrees Celsius, something unexpected happens: the display indicating the electrical resistivity of the mercury drops abruptly to zero. And there it remains. The researchers’ first reaction is that it must be an error. However, subsequent experiments show that they have discovered a new phenomenon. In 1913, Kamerlingh Onnes called this effect superconductivity.

Waiting for Superconductors for Everyday Use

Superconductors have excited the imagination ever since they were discovered. Even Kamerlingh Onnes dreamed of transporting electricity in power grids with no losses whatsoever. The discovery of so-called high-temperature superconductors in 1986 at the IBM research laboratory near Zurich created a great deal of euphoria. The two men who made the discovery, Karl Alex Müller and Johann Georg Bednorz, were awarded the Nobel Prize for Physics as early as 1987. A more sober atmosphere has now returned, however, as has happened so often in the history of superconductors.

Although superconducting technology has become indispensable in basic research, it is encountered on a routine basis only in magnetic resonance imagers, because the complex cooling is expensive. The solution would be superconductivity at room temperature, but such materials have remained a dream. Since 1993 it has not been possible to raise the temperature record any higher. It currently stands at minus 138 degrees Celsius (135 Kelvin) and is held by a high-temperature ceramic superconductor with the complicated name of HgBa$_2$Ca$_2$Cu$_3$O$_8$ (Hg: mercury, Ca: calcium, Ba: barium, Cu: copper, O: oxygen).

Bernhard Keimer relates that company representatives recently asked him when superconductivity at room temperature could be expected. “They were disappointed when I told them that no one had an answer yet,” he says, smiling. The Director at the Max Planck Institute for Solid State Research in Stuttgart and this year’s recipient of the prestigious Leibniz Prize ought to know – after all, he has been researching high-
Superconductors have excited the imagination ever since they were discovered. Even Kamerlingh Onnes dreamed of transporting electricity in power grids with no losses whatsoever.

This is also the motivation for the research being undertaken by Frank Steglich, a Director at the Max Planck Institute for Chemical Physics of Solids in Dresden. The honor of having been awarded the most valuable prize in German science is not all that Steglich and Keimer have in common: both researchers work in the field of “unconventional superconductors,” although Steglich’s team in Dresden works on so-called heavy fermion systems, which become superconducting at very low temperatures.

“In order to understand what unconventional superconductivity means, classical, conventional superconductivity first needs to be explained,” Steglich emphasizes. It was 1957 before the three Americans John Bardeen, Leon Cooper and Robert Schrieffer managed to crack this tough nut. In 1972 they received the Nobel Prize for Physics for this work. The BCS theory – the name derives from their initials – can be understood only by immersing oneself in the physics of solids.

Like most solids, superconducting materials consist of crystals in which the atoms organize themselves into a regular spatial lattice. Nature loves order if it helps to save energy. And the atoms in crystals succeed in doing just that, as they can share certain electrons among each other. These electrons provide the glue, the chemical bond, between the atoms. This works only with the aid of quantum physics: since electrons, as quantum particles, are also spatially extended waves, they can bind neighboring atoms to each other.

In metals and semiconductors, however, not all electrons act only as glue for the crystal. Some of them escape from the atoms and move with almost complete freedom through the lattice, but they require a certain energy to do this in semiconductors. These free conduction electrons carry the electric current. This loss leaves the “atomic cores” with a positive electric charge.

GENTLE VIBRATIONS BIND TWO ELECTRONS

“The conduction electrons can even move through a perfect crystal without meeting any resistance,” explains Frank Steglich. This is due to the uniform arrangement of the atoms: if the distances between the peaks and troughs of the...
The properties of the Cooper pairs are radically different from those of the electrons. Pursuant to the rules of quantum mechanics, electrons possess a half-integer spin. They thus belong to the group of particles known as fermions. These are quite acquisitive, each requiring a quantum state for it alone. In the Cooper pair, the two half-integer spins of the two electrons either subtract to a total spin of zero or, more rarely, they also add up to one.

Quantum particles with integer spin, however, belong to the group of particles known as bosons. Bosons are so sociable that they all like to condense together into one quantum state if the heat energy in the system becomes low enough for this to happen. For Cooper pairs, this is the superconducting state in which many Cooper pairs permeate each other to form one “macroscopic” quantum state. This large quantum object can simply “slip through” the many small flaws in the crystal without noticing them. This is how the electrical resistivity disappears.

“In superconducting cables, this macroscopic quantum state can extend over kilometers,” says Bernhard Keimer. “That’s quite remarkable!”

In conventional superconductors, the Cooper pairs, which have a wide spatial extent, always have a total spin of zero. Decisive for the properties of conventional superconductors are the lattice vibrations, which are slow, com-

1 To gain a better understanding of high-temperature superconductivity, Bernhard Keimer and his colleagues use the apparatus in the far right of the picture to produce thin crystalline layers with customized superconducting properties.

2 Daniel Pröpper and Bernhard Keimer observe how the cryostat in the foreground cools the sample of a high-temperature superconductor that loses its resistivity only at temperatures far below freezing point.
pared to the speed of the electrons, and which bind the two conduction electrons to a Cooper pair. Since crystal lattices vibrate with ever-increasing speed and amplitude as the temperature increases, this destroys the Cooper pairs. Conventional superconductivity can therefore be observed only at relatively low temperatures.

High-temperature superconductors become superconducting at much higher temperatures. They must therefore contain a much stronger Cooper-pair glue in order for the lattice vibrations not to rip the pairs apart. Many indications point to the fact that these quantum superglues function in a completely different way than lattice vibrations. This is thus taken to be the characteristic of unconventional superconductivity. There is still no conclusive theory, but one thing is clear: superconductivity and magnetism act in close collaboration in unconventional superconductivity.

This is surprising, as magnetism is pure poison for conventional superconductors. “A magnetic atom contamination of less than one percent in the crystal already destroys its superconductivity,” explains Frank Steglich. Magnetic atoms introduce an electron into the crystal lattice, whose unshielded spin acts as a small magnet at the site of the atoms. If, in a conventional superconductor, an electron of an extended Cooper pair now passes by, the local spin forces it to reverse its spin appropriately. But this love affair destroys the weak bosonic marriage with the distant “Cooper partner.” If this happens too often, the superconductivity breaks down.

**COOPER PAIRS WITH PARTICULARLY STRONG GLUE**

With unconventional superconductors, in contrast, certain forms of magnetism seem to be really helpful. This also applies to heavy fermion superconductors, which have fascinated Frank Steglich for more than three decades: “We currently know almost 40 of them!” Most heavy fermion superconductors lose their resistivity only at very low temperatures. “If we have around 2 Kelvin, or minus 271 degrees Celsius, we are very happy,” says Steglich’s colleague Steffen Wirth, explaining the challenge. Nevertheless, the Dresden-based researchers hope that such superconductors can also help them contribute to solving the mystery of the gluing mechanism in high-temperature superconductors. But what exactly is a heavy fermion?

The particles can be found in a crystal lattice whose fundamental building blocks always include a magnetic atom: cerium, for example, takes on this role in the cerium-copper-silicon compound CeCu$_2$Si$_2$, in which unconventional superconductivity was first discovered in 1979. The researchers in Dresden know this forefather of the heavy fermion superconductors so well in the meantime that they can adjust its properties when growing crystals: a tiny excess of copper turns it into a superconductor, a small deficit into an antiferromagnet.

In antiferromagnets, the electrons responsible for the magnetism, which in cerium are called 4f electrons after their position in the electronic shell, always orient themselves in the direction opposite to that of the neighboring atom. Their overall magnetic field thus cancels out perfectly on average. This magnetic order is called antiferromagnetism, because it is the counterpart to the ferromagnetism with long-range effect, which takes its name from iron (lat. ferrum).

In CeCu$_2$Si$_2$, as a typical example, the local 4f electrons develop a particularly strong influence on the free conduction electrons at very low tempera-
tured: put simply, they bind them together to form a quantum fluid with the viscosity of honey. The electrons contained therein now sluggishly drag themselves through the lattice – up to a thousand times slower than normal conduction electrons. “These new quasi-particles thus behave like electrons that apparently have a mass up to one thousand times greater,” says Steglich, “which is why we coined the term heavy fermions in the late 1970s.”

The heavy fermions also form the Cooper pairs in such superconductors. Their sluggishness means that the two partners must cuddle up close in order to be able to bond with each other. However, this makes the electrical repulsion between them all the stronger. The glue between them must therefore be much more powerful than in conventional Cooper pairs. This is why it has been clear for more than three decades that the conventional BCS mechanism does not work here.

Although the theoretical physicists proposed alternative glue mechanisms early on, solids are complicated structures comprising enormous numbers of atoms and electrons that exert a reciprocal influence. This makes it very difficult to “take a look inside” them in experiments. Neutrons provide one possibility: these nuclear particles are small and electrically neutral, so they can penetrate matter almost unhindered. Like electrons, however, they have a half-integer spin, which makes them into well-matched little magnets. They thus become probes that react to all electrons with a “free” magnetic moment.

Oliver Stockert, another colleague of Frank Steglich, recently used this method to investigate CeCu$_2$Si$_2$ at the neutron source of the Institut Laue-Langevin in Grenoble. In the process, his team discovered that the magnetic interactions in the lattice were indeed 20 times as strong as the gluing of the Cooper pairs would require. “This is obviously how they make superconductivity possible,” says Stockert. The measurements with neutrons do not provide proof, but the smoking gun, so to speak. His colleague Steffen Wirth is employing further methods in parallel in order to conclusively complete the picture.

**SHORT-LIVED MAGNETIC FIELDS BIND THE ELECTRONS**

This idea is now taking shape. The Cooper pair glue is actually magnetic. Its force originates from spin fluctuations of the heavy fermions. In the general chaos, they form small “bubbles” with short-range magnetic order that form and disappear rapidly. These fluctuations particularly exert their effect close to a state known as the quantum critical point. This point can be reached via low temperatures, the correct chemical mixture in the crystal, magnetic fields or pressure. In CeCu$_2$Si$_2$, two very strong effects are competing with each other: the antiferromagnetic order is fighting against the normal metallic state, which is magnetically unordered. “And if two are busy quarrelling, the third can take advantage of the situation,” says Wirth. Steglich adds: “Very strong spin fluctuations that produce Cooper pairs occur especially at the point where the two cancel each other out.”

With spin fluctuations, the particles involved waggle their spins and influence each other in this way – a disrespectful way of putting it. The short-lived magnetic fields created in this way are sufficient to strongly bond the electrons to form Cooper pairs. Spin fluctuations also play a crucial role in high-temperature ceramic superconductors. Most, if not all, of the physicists conducting research in this field are convinced of this, says Bernhard Keimer – and he includes himself here.

“Although here we have only one electron system, unlike the heavy fermion superconductors,” he explains. This means that there are no local 4f electrons here to create a tendency for latent antiferromagnetism. Instead, it is only the conduction electrons that bring about the interaction between magnetic order and superconductivity.

Most copper oxide compounds, including the high-temperature superconductors, are even insulators. Their complex crystal lattice has a sandwich-type structure. Layers of copper and oxygen atoms play a crucial role in this process, which is why these brittle materials are called cuprates. The Cooper pairs move along these copper oxide...
planes, so their superconductivity is strongly two-dimensional – “flat,” as it were. The conduction electrons required are provided by foreign atoms with which the researchers intentionally contaminate their crystals.

Bernhard Keimer uses diagrams to show how the superconductivity probably operates in cuprates. In the copper oxide planes of the crystals, certain electronic states of the copper atoms overlap each other. These “d-orbitals” form the racetrack for the conduction electrons. The electrons tend to a fluctuating antiferromagnetic order when approaching the superconducting transition temperature: they orient themselves antiparallel as they get closer to it.

If an electric current now flows, individual conduction electrons must migrate through this spin landscape. The rules of quantum physics require them to continuously flip the spin of the electrons they encounter to suit their own spin. “They leave behind a trail of flipped spins, which is very energy intensive,” explains Keimer:

“Their motion through such an antiferromagnetic background is very slow!” The electrons can save the energy they expend here by forming Cooper pairs – which are very small, as they are in the case of the heavy fermion superconductors. With their total spin of zero, they become invisible, as it were, to the antiferromagnetic stubble field of half-integer spins. They slip through without losing any energy whatsoever, and the cuprate becomes a perfect electrical conductor.

**RESEARCH SHOULD SOMEHOW BENEFIT SOCIETY**

“It is still just an idea for a model,” says Keimer with a smile. A Stuttgart-based team headed by his colleague Vladimir Hinkov used neutrons at the FRM-II research reactor in Garching and observed that strong spin fluctuations actually do occur. They input the measurement data without “fine-tuning” into a model being developed by the theoreticians in Stuttgart, explains Keimer. This then computed a transition temperature at which the substance would theoretically become superconducting. The first shot at 170 Kelvin was almost twice as high as the substance’s real transition temperature, but Keimer considers this result to be very encouraging: “The closer one looks, the simpler the picture gets.”

The researchers in Stuttgart have also perfected the production of artificial crystals, which they now want to use to imitate the layer structure of the cuprates. They hope this will take them a few more steps along the learning curve. “It is possible to make great progress in high-temperature superconductivity with simple models,” states Keimer optimistically. These findings may one day contribute to developing a material that conducts current at room temperature with zero resistivity. Bernhard Keimer keeps this long-term objective in mind. “As a basic researcher, I have a vision, of course, that this research will benefit society one day.”

**GLOSSARY**

**Transition temperature**

The temperature below which a material becomes superconducting.

**Fermion**

A particle with half-integer spin; fermions such as electrons each require a quantum state of their own.

**Heavy fermion superconductors**

The unpaired electrons they contain, which in some metals stay very close to the atomic nucleus, contribute to superconductivity. They therefore move extremely slowly, which is why they appear heavier than they actually are.

**Cooper pair**

Two electrons that are fermions combine to form a Cooper pair and become a boson. At sufficiently low temperatures, a very large number of Cooper pairs occupy a quantum state in which they no longer experience the flaws and vibrations of the crystal – the resistivity disappears.

**Bosons**

Particles with integer spin; unlike fermions, they all occupy a single quantum state in the ground state.

**Spin fluctuations**

The spin or intrinsic angular momentum gives the electron its magnetic moment. The orientation of the spin thus determines the magnetic order in a material. Even before it assumes a certain magnetic order – ferromagnetic or antiferromagnetic, for example – this order can already form temporarily in some regions because the spins fluctuate – that is, change their orientation.
Histones are important proteins for epigenetics. Consequently, delegates at the Epigenetics Conference are greeted with the amino acid code of the histone protein H3.
The different types presented by Shelley Berger display an amazing variety. “One is a typical command receiver,” explains the cell biologist, “while the next one tells the first what to do.” And the third is not only the boss – on top of that, it lives a lot longer than the others and is the only one that is fertile. Although it is not too surprising that such differences occur, what is astonishing is that the three types have identical genomes. Yet the lively speaker from the University of Pennsylvania, USA, is not presenting a study on triplets or cloned breeding animals. She is describing natural processes exhibited by the Florida carpenter ant Camponotus floridanus. The behavior and the physical form of the insects in the three boxes display marked differences. And these are not even remotely genetically fixed.

But what else could have such a strong modifying effect on the mind and body? There are structures in the genome that, while having no effect on the genes themselves, still determine which of them can use a somatic cell and which can’t. These structures define the way a cell is built and how it functions by means of a gene activation program. Berger shows what this does to the ants. She states that, in the genome of brain cells, there are systematic, non-genetic differences that ensure that the subordinate female worker ants are more sensitive than their dominant sisters to their inhibitory messenger substances.

A SENSE OF EXCITEMENT IN THE FIELD OF EPIGENETICS

Epigenetics as a research field focuses on the ingenious mechanisms that underlie gene regulation. There is scarcely a scientific discipline that is developing as rapidly as this new branch of genetics. And with good reason: epigenetic structures affect practically every life form – they are the memory and
fying their epigenome. They can, as it were, recall former states induced by external stimuli and store them. For example, an early childhood trauma in humans can trigger the permanent reprogramming of brain cells and make an individual prone to depression decades later. Or over-nutrition in the womb can alter metabolic cells to the extent that an individual will be more likely than other people to develop type 2 diabetes in old age.

Shelley Berger does not have to explain these things to her listeners. They are experts in the field. Early in December 2010, she spoke to an audience of more than 100 from around the world at the first Max Planck Freiburg Epigenetics Meeting. In three days alone, 40 lectures were given at the Max Planck Institute of Immunobiology and Epigenetics. A significant number of them were presented by world-renowned specialists such as Phil Avner, Geneviève Almouzni, Amanda Fisher, Edith Heard, Barbara Meyer, Steve Henikoff, Gunter Reuter, Wolf Reik, Yang Shi, Brad Bernstein, Martin Vingron, Danny Reinberg, Roland Schüle, Susan Gasser and Meinrad Busslinger.

Each of the lectures was subsequently discussed in unusual depth by the experts, who generally focused on biochemical details. But the burning issues surrounding epigenetics really came to a head in conversations held away from the formal setting. Researchers pondered over lunch whether the tofu in the vegetarian dishes provided protection against cancer via an epigenetic mechanism. And they wondered over dinner whether a substance called resveratrol in red wine could have a life-prolonging effect given that it can, at least in a test tube, epigenetically halt cell aging.

EPIGENETICS INFLUENCES MANY ILLNESSES

This difference – hard-core molecular biology on the one hand and possible solutions to humanity’s great issues on the other – illustrates the fascination that this new discipline inspires. The science is unbelievably complex, but it is also well on its way to making life both easier and better for humans. “There is a direct link between the body’s metabolic processes and the identity marker of every cell. Their influence penetrates into the very essence of life, even in us humans.

EVEN ACQUIRED FEATURES CAN BE INHERITED

Just five years ago, quite a number of biologists had no idea what epigenetics meant. Today, even doctors, educationists, psychologists and politicians are familiar with the term. The Greek prefix ‘epi-’ means ‘subsidiary’, ‘additional’ or ‘over’. In fact, epigenetics is a sort of “additional genetics,” associated by definition with everything that a cell passes on to its daughter cells by way of residual information over and above the DNA base code. Once a so-called epigenetic switch has been set in response to an external stimulus – such as a developmental signal – it determines, for example, whether a cell will form part of nerve, skin or liver tissue.

The sum of all of the switches forms the epigenome of the cell, and each cell has its own specific epigenome, which it passes on when the cell divides. However, cells also respond to their environment by modifying their epigenome. They can, as it were, recall former states induced by external stimuli and store them. For example, an early childhood trauma in humans can trigger the permanent reprogramming of brain cells and make an individual prone to depression decades later. Or over-nutrition in the womb can alter metabolic cells to the extent that an individual will be more likely than other people to develop type 2 diabetes in old age.

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epigenetics of metabolic cells,” claims Paolo Sassone-Corsi from the University of California in Irvine, USA. He is investigating the inner clock, a vivid example of this link.

There is a clock ticking in every cell, he says, and it has the genome firmly in its grip. “The activity of at least 15 percent of the genes in a cell oscillates in a 24-hour rhythm.” He and his team have just discovered an epigenetically active enzyme associated with this clock. It translates the time sense of the cells into a gene activation program. Called MLL1, it binds to proteins that act rhythmically and determines the time of day at which some genes can be read and others can’t. It is now known, says Sassone-Corsi, that when the inner clock is disrupted – which can occur, for example, when a person does regular shift work – conditions are more favorable for diabetes and many other metabolic disorders.

Tests show that genetically identical mice fed with the same food either become ill or remain healthy depending on whether they get the food at the right time or not. There is much to indicate that such disruption alters the “epigenetic memory” of the cells and thus upsets the equilibrium of the whole body, rendering the individual susceptible to illness. “Epigenetics touches many different fields. It starts with nutrition and ends with trauma,” believes Herbert Jäckle from the MPI for Biophysical Chemistry in Göttingen.

NEW TREATMENTS FOR STRESS DISORDER

The Ministry of Defense is now interested in the epigenetic explanation for post-traumatic stress disorder as well. “Increasing numbers of soldiers are returning from foreign deployments with this disorder.” There is felt to be an urgent need for new treatments, and epigenetics might be able to deliver them. The time is now ripe, he says, not least because of the recent findings, to take a proactive approach to advance the discipline. That is why the Max Planck Society supports the Freiburg Meeting, and also why it resolved to expand the work of the city’s Max Planck Institute for Immunobiology and change its name to refer to both epigenetics and immunobiology.

The new name was announced the day before the conference, an occasion that could not have been better and one that had been long awaited by co-organizer Thomas Jenuwein. Back in 2008, when the epigenetics pioneer was appointed Director at the Freiburg Max Planck Institute, he said, “We are standing on the threshold of a new way of thinking in biology, on the threshold of the post-genome society.” The glorious age of genetics lasted five decades, he pointed out: “It began in 1953 with the announcement of the DNA structure and ended in 2003 with the publication of the almost complete human DNA sequence.” In saying this, Jenuwein in no way wishes to diminish the extraordinary achievements of the geneticists. Rather, he is keen to build on their findings to drive biology forward and reveal what is passed on over and above the genes.

There are different epigenetic switch systems. For example, if methyl groups are bound directly to DNA (DNA methylation), that generally inactivates the affected gene. Changes to the histones are a great deal more variable. Histones are proteins around
changes to histones regulate gene activity

“More than 50 histone modifications are now known,” says Robert Schneider, though “we can hardly be anywhere near the full total yet.” Schneider, who became head of an epigenetics group at the Freiburg Max Planck Institute as early as 2004, introduced conference delegates to a previously unknown chemical modification in the nucleosome center. Until now, it was especially the so-called termini of the histones, which project out of the nucleosome like tails, that had been regarded as the main access point for modifications. Apparently the experts need to think again: “The histone modification that we discovered probably opens a window that gives enzymes access to a DNA binding site,” explains Schneider. Discoveries such as these might even help fight diseases that are very difficult to treat, stresses the epigeneticist.

It has long been clear that cancer and many other illnesses are linked to wrongly regulated epigenomes, he says, so every newly discovered epigenetic switch provides a potential point of attack for future medications. This is because, unlike gene mutations, wrongly configured epigenetic switches can, in theory, be returned to their previous configuration. Cancer researchers in

“we are more than the sum of our genes”

Thomas Jenuwein is regarded as a pioneer of epigenetics. In 2000, he and his team discovered the first enzyme that, in humans and mice, deposits methyl groups on histones, effectively switching off genes permanently. The molecular biologist has been a Director at the Max Planck Institute of Immunobiology and Epigenetics in Freiburg since 2008. His research field is having a profound impact on contemporary biology, as Jenuwein reveals in an interview. The staggering discoveries in epigenetics and their enormous implications are already transforming society today.

Mr. Jenuwein, you say that we are living in a post-genomic society. Why?

Thomas Jenuwein: Because we have decoded the human genome and are forced to acknowledge that we are more than the sum of our genes. The DNA sequence taken in isolation is not enough to provide a full explanation for either normal or aberrant development. We are now in the age of epigenetics and chromatin – the unit composed of DNA and the attached proteins. It’s all about understanding cell identity from a functional perspective.

So your science is now acknowledged as such? Absolutely. You need only count how many studies are published on epigenetics. Whereas there used to be no more than 400 per year, there are now around 8,000.

How did this development come about? The key breakthrough was the discovery of the enzymes that chemically mark chromatin. That led to an explosion of new avenues of research. This was because the discovery created a pathway to controlling genetic activity, to cell identity and to different chromatin states. The main thing, however, was that we finally understood how changes in metabolism and energy consumption, as well as changes caused by environmental factors, could have a lasting effect on cells – it was because they could be transferred to chromatin via enzymes and their cofactors.

So epigenomes really do give cells a memory? Will we be able to manipulate this memory one day?

Our recognition of the way enzymes modify chromatin has opened up potential ways of doing this, because enzymes can be inhibited. And this takes us to the heart of treatment approaches. Take cancer, for
particular have high hopes for this new science – provided the epigeneticists can shed light on other fundamental principles. There is a new experimental model that may help: Herbert Jäckle is using it in a bid to systematize the world of histone modification. “The term histone code signifies nothing more than the fact that, in certain combinations, certain markings on the histones cause certain phenomena. This is the very thing that we want to test now.”

In his sensational main lecture, Jäckle presented the latest findings on the fruit fly *Drosophila*. The genome is an example. Clinics already have such substances as HDAC inhibitors and DNMT inhibitors. Treatment based on epigenetics is already a fact of life in cancer research.

Are there other examples? Epigenetics also helps in reprogramming somatic cells to become stem cells. I am convinced that, in five years’ time, we will have a success rate of 40 to 50 percent in this field – and it will be thanks to the specific influence of epigenetic enzymes. At present, the success rate is only 1 to 2 percent. The third point is the continued expansion of our understanding of how dietary habits and stress signals affect the epigenomes of cells. This opens up quite clear avenues toward a new kind of prevention.

This is somewhat reminiscent of the promises – as-yet unrealized – held out for the human genome project, that is, new and effective treatments for the major widespread diseases. Why do you think we are now closer to that goal?

Because we know the interrelationships. We know what makes the chromatin in a stem cell different from that in a mature cell. Looking at the epigenetic markings on chromatin, I can now see how old a cell is, what type of cell it is and whether it is healthy or not. So we have our fingers on the right switches. This ultimately means that any conceivable thing in this field is possible. In theory at least, diabetes cells can be made fully functional again, malignant cancer cells can at least be made more benign, and brain cells can be made less susceptible to stress.

Is DNA unimportant, then? The driving force in the cell continues to be the DNA sequence, without question. But the crucial factor is that we can modify epigenetics. Adrian Bird once said that even if epigenetics affected only 0.1 percent of development, it would be absolutely sufficient – given the huge number of human cells and cell types – to reconstruct all sorts of adaptations, both good and bad.

The Max Planck Society has itself recognized the significance of the new science and changed the name of the Freiburg institute to incorporate both immunobiology and epigenetics. Are you proud of this? Naturally. But it was also a logical development that began long before my time in Freiburg. Immunobiology and epigenetics are inextricably linked. The first Epigenetics Research Group has been at work here for five years. The key thing is that researchers at Freiburg understood very early on how innovative epigenetics was. Next came the call for applications, the new building and the inauguration of a new department, which I was asked to head. In addition, arrangements were made for Davor Solter – co-discoverer of imprinting and a pioneer of modern epigenetics – to be succeeded by Asifa Akhtar, an outstanding epigeneticist. And then the institute was renamed – more or less as a beacon to the world.

Interview: Peter Spork

The conference organizers: Asifa Akhtar holds a chromosome model, while Thomas Jenuwein wears a representation of chromatin with epigenetic modifications around his neck.
a storehouse for quite a number of gene copies, several hundred in the higher organisms, which are needed for the production of histones. This explains why it was previously thought impossible to switch off these gene copies and replace them with genetically modified histone variants. Jäckle’s team removed all the histone genes from the flies, which caused the insects to die off after the fourteenth cell division. However, following the introduction of a critical number of gene copies, the flies regained their ability to survive and reproduce. In the next stage, the Göttingen-based researchers want to return particular histone genes to the insects. These genes have been modified to the extent that they lack docking sites, for example, for certain chemical groups. This would prevent certain histone modifications. “That would enable us to work through the histone code section by section to identify which biological effect is produced by which histone markings,” explains Jäckle.

**RNA FRAGMENTS SILENCE GENES**

There is another important epigenetic switch system, the non-coding RNAs, or ncRNAs for short. The very sections of DNA that geneticists used to regard as functionless and refer to disparagingly as “junk DNA” actually code for these RNA fragments. They are, as it were, siblings of the messenger RNAs and, though a little underdeveloped, are definitely not junk. But unlike messenger RNAs, they do not contain instructions for producing proteins. On the contrary, one of their tasks is to remove from circulation any messenger
RNAs whose base code matches their own. Accordingly, the transcript can no longer be translated into a protein and the effect of a gene is thus weakened or even completely silenced. Known as RNA interference, this principle, discovered in 2006, was honored with the Nobel Prize for Medicine. These days, almost every week sees the publication of new studies that demonstrate the importance of these processes in, for example, the prevention or the development of cancer.

Ingrid Grummt from the German Cancer Research Center in Heidelberg reports in Freiburg on another of the tasks of ncRNAs. She discovered ncRNAs that attach themselves near a gene to a DNA strand that matches their base sequence and, in doing so, insinuate themselves solidly into the DNA double helix. This produces a triple helix. Enzymes, in turn, bind to this structure and attach a methyl group directly to the DNA, thus silencing genes. Since more than half of the human genome can be transcribed into ncRNAs, Grummt suspects she has discovered a very general mechanism. “It is certainly conceivable that all genes that are silenced for any length of time have precisely matching ncRNAs,” she says. There’s no doubt whatsoever that epigeneticists are in the grip of gold fever.

“Just now, our field of research is getting increasingly complex and difficult to take in,” explains Renato Paro from the Department of Biosystems at the Technical University of Zurich. His colleague Peter Becker from Munich’s Ludwig Maximilian University concurs, saying, “The more research I do, the less I understand.” He is delivering a paper on a problem that faces all living creatures that determine their sex via sex chromosomes. They need to ensure that genetic activity is organized on a balanced basis. In humans, for example, women, unlike men, have two X chromosomes. Without compensation, the genes lodged there would be twice as active in women. That is why one X chromosome is switched to be epigenetically silent in all female cells.

“We used to think that all organisms did this in the same way,” says Asifa Akhtar, head of the Laboratory of Chromatin Regulation at the Freiburg Max Planck Institute. But the epigenetic toolkit is way too variable for nature not to have found other solutions as well. “Drosophila, for example, does the opposite. In these creatures, the X chromosome activity in males is nearly twice as strong,” explains Akhtar. She is investigating proteins that are involved in this regulation, but that also play a role in human epigenetics.

BETWEEN IMMUNOBIOLOGY AND EPIGENETICS

One of her objectives is to compare the epigenetics of humans and flies. Ultimately, she is as concerned as most of her colleagues to get to the bottom of this complex new field of research, as far as this is possible. In this sense, the Freiburg Meeting, organized jointly by Asifa Akhtar and Thomas Jenuwein, Monika Lachner and other colleagues, might well have helped already. “It all went off so well, it was a wonderful start. We managed to get Freiburg on the epigenetic research map,” she says, summing up the outcome. “And now we will try to repeat the meeting every two years in December.”

Immunobiologist Rudolf Grosschedl, current Managing Director of the Freiburg institute, is also keen on the idea of repeating the conference. “We would very much welcome this, preferably alternating it with a conference on immunobiology.” On the whole, everyone was “thoroughly satisfied” that they managed to bring epigenetics to Freiburg. This field, he says, enriches key research areas of the future and is also indispensable for immunobiology.

Most of the epigeneticists would like to return, that much is clear. Shelley Berger would then probably be able to provide fresh reports from the ant kingdom. One of the questions might be why some people – similar to ant queens – live very much longer than others. For, as Berger knows, “ants are a wonderful model for studying aging processes.”
Almost every morning at around 7:00 a.m., a man cycles five miles through the hilly fields of central Hesse from the small municipality of Biebertal to the somewhat bigger town of Giessen. Spring, summer, fall and winter. Not even sub-zero temperatures and snow-covered paths and streets can deter him. After all, he has spikes for the wheels. He stops his vehicle at the Director’s parking spot at the Hospital for Internal Medicine at the Giessen campus of the University Hospital of Giessen-Marburg. The man is the Director and one of today’s most renowned lung specialists.

THE MIRACLE OF BREATHING FREELY

Werner Seeger, a tall, slim man with boundless energy, looks very different from many other university chiefs of medicine in this country – and not only because, whenever possible, he travels by bike rather than driving a prestigious limousine. Of course, that alone says a lot about him. He is the only chief of medicine of a university hospital who is also employed as a Director at a Max Planck Institute, the Max Planck Institute for Heart and Lung Research in Bad Nauheim. When necessary, he thinks outside the box when it comes to science. He has crucially raised awareness about pulmonary disease – for decades a neglected problem – among the public and those who allocate research funding. He speaks often and in equal measure about luck and purpose when he talks about his career. “As doctors, we have a mandate to do everything possible to maintain the miracle of breathing freely,” he says. And yet, after more than 30 years of daily hospital life, it seems to an observer that, despite his huge success as a doctor and researcher, he still has not lost his concern for patients. These are people who are often anything but highly educated academics, with extremely serious health problems, at the threshold between life and death.

The advances made by Werner Seeger and his team in the treatment of pulmonary hypertension mean that many patients at least live longer, with a better quality of life. This, however, is not enough for the Director at the Max Planck Institute for Heart and Lung Research in Bad Nauheim: the dedicated doctor and researcher wants nothing less than a full cure for this disease.

TEXT KLAUS WILHELM
Nor is it any different this morning at 8:00 a.m. when we visit the general ward. At this time, he has already spent half an hour in the intensive care unit (ICU). He talks about two younger patients who are in an induced coma there as a result of the H1N1 swine flu virus. Their lungs are extremely damaged due to a massive acute infection, and they therefore had to be put on an artificial lung machine. “Their chances of survival are not very good, unfortunately,” says the 57-year-old: “This is the reality in which I live.” He says it as if he takes the powerlessness of modern medicine in such situations personally, and the suffering of his fellow human beings as an incentive to keep going to alleviate the distress of patients with serious lung diseases. “At the end of my career, I would be happy to have it said about me that I contributed significantly to this,” he says.

Extreme situations are part and parcel of life in the Giessen Lung Center, even in the general ward. Mr. L. has announced that he intends to end his life. He is serious. He suffers from a deadly pulmonary disease about which laypeople, even those who have an interest in medicine, know very little: pulmonary fibrosis. His only chance was a lung transplant. After an agonizing one-year wait, doctors performed the transplant a few months ago and he initially responded well to the donor organ. Then he deteriorated again. The new organ is prone to constant infection and his lung function can’t be stabilized. Now his bronchial tubes seem to be narrowing and he suffers increasingly from shortness of breath. His wife has left him.

Seeger takes a deep breath. This case has affected him personally. Nevertheless, he analyzes the patient’s medical data calmly and objectively in the presence of the ward physicians and medical students. “The patient is considering a rational suicide,” explains the doctor. The man is reflective, of sound mind and does not want a psychiatrist. The doctors can’t force him to see a psychiatrist. “He’s right. His situation is very serious,” says Seeger, who nevertheless believes there is still a chance of stabilizing the donor organ with a different antibiotic treatment and by widening the narrowed bronchial tubes.
bronchial tubes using an endoscopic procedure. “This is what I will be proposing.” On Saturday, after spending Friday in Paris, where leading experts are preparing the next world congress on pulmonary hypertension, he will speak to Mr. L. privately.

FOCUS ON PATIENTS

Regardless of how difficult it may sometimes be, talking to patients is important to the professor. As he does his rounds, which last two hours today, he always adopts the right tone, makes a joke whenever possible, and delivers clear messages whenever necessary. He offers one patient, who is being treated as an in-patient for the 25th time in Giessen, a ticket for the opening ceremony of the new university hospital. He comforts another patient who is on the waiting list for a donor organ. The professor speaks clearly, in a language that people understand. “Each patient must feel that they are treated as an individual, taken seriously and accepted.” This is how he describes his approach as a healthcare professional. “It is more a question of basic attitude than the length of the conversation. When I speak with patients, I try to give them my complete attention.” Seeger also endeavors to be a role model for younger doctors, which is extremely important: “This isn’t something that you can learn in lectures, and certainly not in multiple choice tests.” He knows that none of this is easy in the daily routine of a hospital: focusing on patients and at the same time protecting oneself from the daily suffering and the constant presence of death. “You really have to maintain a balance if you want to do your job well.”

Seeing how he deals with patients would indicate that his past plays a role in this. Seeger comes “from a very modest background,” as he puts it, growing up on a small farm in eastern Westphalia. When it came to choosing a career, becoming a teacher was the extent of his parents’ imagination. This would have meant that he could also still work on the farm. But it was not to be. “I wanted a career that involved people,” he says. Studying theology was thus one consideration for the devout Protestant. Medicine was the other, ultimately more attractive, alternative, “because there I could do something more concrete, more practical for people.” He was also seized with enthusiasm for research, a passion that he still retains today.

10:00 a.m.: The professor switches to his second world – science. Compared to his medical rounds, this is a radical change to a world of highly academic ideas and conversations, a micro- and nano-world of cells and molecules and intense debate, conducted in English of course, with doctoral students and young biomedical scientists from all over the world. “I feel lucky to be able to work in both of these worlds and to bring them together,” he says. It is mainly thanks to Werner Seeger that Giessen currently enjoys an excellent reputation in pulmonary disease research. Worldwide. Up until the mid-1980s, however, pulmonary medicine tended to languish at the University Hospital of Giessen. Then the breakthrough came: with a clinical research group from the German Research Foundation (DFG) and a professor for “respi-
Brains are racked. His tone is positive and measured. The ambitious young scientists may want to impress with the necessary detailed knowledge, but Seeger, with decades of experience in many areas, is often the only one who is able to understand the findings in such a way that the team makes progress. “The different areas complement one another wonderfully,” he says, frankly admitting that, without the symposiums, he would lose touch with emerging technology and the latest findings in molecular biology. “I benefit enormously from them.” Ultimately, he is concerned with understanding what happens at the molecular level when pulmonary diseases develop, and which of the signaling paths involved can be tackled using active agents.

Up until a few years ago, for example, transplantation of a donor organ was the only treatment available for pulmonary hypertension. At a global level, 100 million people suffer from some form of the condition. In their pulmonary hypertension outpatient clinic – the largest of its kind in the world – the Giessen-based experts frequently treat young women with the condition, often after pregnancy, “many of whom I have seen die under my care,” says Seeger. That is something that is not easy to shrug off. This is not the only reason why the team in Giessen has been devoting a large amount of resources into researching this disease since the 1980s.

Pulmonary hypertension is a disease of the lungs’ blood vessel system. In this pulmonary circulation system, as it is known, carbon-dioxide-rich, oxygen-depleted blood leaves the right side of the heart and enters the pulmonary arteries. The arteries divide into pulmonary air sacs (alveoli), where the blood is enriched with oxygen, and the carbon dioxide generated in the body is released. The oxygenated blood flows back to the left side of the heart, from where it is pumped around the body. In the case of pulmonary hypertension, the blood pressure in the blood vessels of the pulmonary circulation system increases, sometimes without any discernible cause, frequently as a result of other illnesses. The vessel walls thicken.
en, “mushroom” inward, and the lumen for the blood flow shrinks. As a result, the right side of the heart has to work harder and harder to pump the blood through the lungs and increasingly decompensates. This poses the threat of heart failure.

Under the aegis of Werner Seeger, the turning point in the treatment of pulmonary hypertension came after decades of stagnation. “Here at the Lung Center in Giessen, we have brought three drugs from basic research to worldwide approval,” says the researcher and doctor proudly: “That is more luck than a scientist can expect to have.” And the 57-year-old is a team player through and through. He immediately points out that it was primarily his colleagues Friedrich Grimminger and Ardeschir Ghofrani who discovered a treatment for pulmonary hypertension based on the impotence drug Viagra. In cell and animal experiments in the laboratory, researchers at the Lung Center had proved the significance of the molecule phosphodiesterase-5 in pulmonary hypertension. At the same time, the pharmaceutical industry had launched Viagra as a treatment for erectile dysfunction. The drug contains an active agent that inhibits phosphodiesterase-5. “It seemed logical to us that Viagra would also have to dilate the narrowed pulmonary vessels, which subsequently proved to be the case in animal experiments.”

**NEW APPLICATION FOR VIAGRA**

The researchers in Giessen embarked on an extraordinary study to prove that the same happened with people. At heights of about 16,500 feet and above, everyone suffers from pulmonary hypertension, which returns to normal once the person comes back to lower ground. So the doctors sent a group of mountain climbers and a suitably complex medical measuring device to Base Camp at Mount Everest. By yak! After a few days, they determined the expected high lung pressures of the test subjects, which also increased further under stress, and in this study proved the effectiveness of Viagra in reducing pulmonary hypertension in humans. The active agent was officially approved in 2006 following an international, multi-center study initiated by the Giessen Lung Center on people with severe pulmonary hypertension. It has since been approved worldwide. Seeger and his colleagues had already been treating critically ill patients “off-label” with Viagra for years – always following tough discussions with the health insurance companies.

The most recent victory in this series of successful drug developments for treating pulmonary hypertension is the aerosol application of Treprostinil. The Giessen Lung Center in Bad Nauheim also provided the research basis for the active agents Riociguat and Imatinib, which are currently being tested in major clinical studies. Riociguat stimulates an enzyme, soluble guanylate cyclase, that plays a role in regulating stress in pulmonary vessels, as well as in regulating growth. Imatinib is already used in cancer treatments and inhibits a growth factor known as PDGF for short. It is a factor in the aggressive growth of tumors, but also in the “pseudo-malignant proliferation of the pulmonary
vessels, which closes the lumen,” as Seeger says. Several active agents are now available. More are expected soon – the more, the merrier. This means that many patients can live more than 20 years with their condition.

**PULMONARY HYPERTENSION CAN BE CURED – BUT HOW?**

“Undoubtedly a revolution,” says the Max Planck researcher, who seems only partly satisfied. “Our goal must be to cure pulmonary hypertension, nothing less will do.” After all, there is at least some proof that the phenomenon of “pseudo-malignant proliferation” of the pulmonary vessels is reversible. Reverse remodeling – reversing the pathological process to a normal vessel structure – is the concept that fires the researcher’s imagination. “Experimentally, we are making progress,” explains Seeger. In other words, the scientists are working hard to find substances and other ways of specifically influencing the signaling paths that control growth in the vessel walls of the lungs and thicken them.

Seeger has similar goals when it comes to researching pulmonary fibrosis. Some 750,000 people suffer from this disease in the EU alone. Of those, 400,000 suffer from the usually aggressive, rapidly progressing, idiopathic form. Its molecular basis is still widely unknown compared to that of pulmonary hypertension. With pulmonary fibrosis, excessive connective and scar tissue forms, destroying the architecture of the alveoli. The lung can dilate less and less and its function deteriorates, with the result that, at some point, the gas exchange no longer functions. Those affected find it difficult to breathe and are constantly prone to new infections and asphyxia. In the final stages of the illness, even speaking is difficult.

In Giessen and Bad Nauheim, researchers are examining what drives the pathological process. Among other things, growth factors such as TGF-beta and FGF-10 play a critical role. Werner Seeger doesn’t yet want to talk about a breakthrough with the first long-awaited effective treatment against idiopathic pulmonary fibrosis, nor about ARDS, the serious lung failure case requiring mechanical ventilation in ICU. No less challenging is the research of the chronically obstructive pulmonary disease of emphysema, in which the small pulmonary alveoli are gradually destroyed. Using stem cells, the researchers are trying to regenerate the lost tissue.

And, in fact, mice that have one lung removed regenerate their pulmonary alveoli completely, in the same way that amphibians can generate a lost tail. Young people can also regenerate their alveoli to a certain extent, with recently discovered pulmonary stem cells probably driving the process. “We successfully stimulated this regeneration of lung tissue in mice in the lab, and it would be fantastic if we could replicate the process in our patients,” says the scientist, as he moves briskly from the excellence cluster meeting to his next appointment around midday. He rarely stops for a break during his long working day. His day is jam-packed, but he never appears stressed. “I try to stay relaxed,” he says. “Of course, I do feel stressed, but usually it is a positive kind of stress because I enjoy my work.”

His third role awaits him, that of medical executive director of the University Hospital in Giessen-Marburg. He visits the university hospital’s new building. “This is the biggest building that was ever built in Giessen,” says Seeger. “We are getting a brand new hospital with 1,200 beds.” It is due to open in four weeks. Thinking about it,
however, makes even a laid-back character like Seeger slightly nervous. Hundreds of patients will have to be moved within a short space of time, including the artificial respiration patients from ICU, together with the machines that they are connected to. Just two weeks ago, cables were still hanging from the ceiling in the admissions area. But now, the large space already looks more inviting. Seeger breathes a sigh of relief and appears somehow delighted as he scrutinizes the modern, high-tech spaces in the future intensive care units. It is apparent that this is a dream come true for him. “Patient management is entirely electronic,” he gushes, instructing staff to perform a detailed function test on every single workstation before start-up. “Nothing dare go wrong, nothing,” he mutters almost imploringly to himself.

1:00 p.m.: Patients are waiting in the outpatient clinic in the lung hospital. Seeger returns to his role of doctor. He doesn’t need to wear the symbolic white coat to radiate authority, a short-sleeved shirt will do. Despite his triple workload, he doesn’t forget to eat. A salad – “healthy nutrition and exercise are important,” he says and relates how, together with his wife, he has been involved for a long time in the German equivalent of Sunday school in his area, occasionally delivering a sermon in the Protestant university parish. His family, including his three children and four grandchildren, is central to his life: “I couldn’t do my job without them.”

FROM THE HOSPITAL TO THE RESEARCH INSTITUTE

3:00 p.m.: Following another appointment in the hospital’s administration office, Seeger sets off for nearby Bad Nauheim. The second research focus of the day is pending in the Max Planck Institute. A colleague reports on his experiments using human induced pluripotent stem cells, or iPS cells for short, in the manufacture of skin cells lining the interior of blood vessels. The goal is, at some stage, to use these cells in patients with pulmonary hypertension to induce the production of new “healthy” pulmonary vessels. However, the researchers first need to resolve a myriad of small problems that stand in the way of the ultimate goal. This is followed by a session in a small group designed to structure a research field that is still young: the investigation of the molecular mechanisms that encourage tumor growth in chronically inflamed lung tissue.

7:00 p.m.: Back to the hospital in Giessen, this time to his desk: e-mails, letters, loose ends and a few urgent phone calls. Finally, back to where the working day began, to a critically ill patient in ICU. Night has long since fallen on this March day when a man gets back on his bike and cycles through the fields of central Hesse. Fourteen hours as a doctor and researcher have come to an end. Until tomorrow at 7:00 a.m.
The Nanoworld
Is Starting to Roll

Nanoparticles on the move: A model representation of two triptycene molecules that are joined by an axle and are capable of rolling.
Imagine vehicles that are just a few nanometers large and that clean surfaces or build molecular structures like tiny vehicles at a construction site. To bring this idea, or that of molecular electronics, out of the realm of imagination and into the real world, physicists working with Leonhard Grill at the Max Planck Society's Fritz Haber Institute in Berlin are investigating the physics of the nanoworld – and they enjoy taking turns at the wheel.

Alex Saywell, a staff member in Grill’s research group, sets a spindle at the end of the long cylinder in motion. With a metallic drone, it slowly pushes a sample into the scanning tunneling microscope. Saywell previously cleaned the fingernail-sized piece of metal, then bombarded it with ions and heated it. Now it isn’t just shiny, it is absolutely pure. Later, custom-tailored molecules – components that the physicists want to analyze and use to begin their Lego game – will be deposited on its surface.

The scanning tunneling microscope enables us to look at or analyze individual atoms,” says Leonhard Grill. This is made possible by the microscope’s fine metal tip, on which, ideally, just a single atom sits. At a distance of about one nanometer, it traverses the sample surface row by row. An electric voltage allows the physicists to measure how much current flows between the microscope and the substrate. “The ingenious trick of scanning tunneling microscopy consists in the fact that this current is extremely dependent on the tip’s distance from the surface,” says Grill. If, for example, it passes over a molecule on the surface, the current increases sharply.

A fully automatic standard scan takes a few minutes. A very good image may sometimes take 20 minutes to complete. In the meantime, a colorful image appears line by line on the at...
The different colors represent the intensity of the measured current – and thus the contours of the surface. Even the untrained eye can recognize the individual atoms of the metal layer and the molecules lying on it.

But the scanning tunneling microscope lets the scientists do more than just look at the molecules: the fine tip becomes a mini finger that pushes the particles around. The first time this was done was in 1990, by physicists in the IBM research lab in Almaden, California, who wrote their employer’s name with xenon atoms. Five years later, researchers at the Free University of Berlin succeeded in reproducing the silhouette of the Brandenburg Gate with individual carbon monoxide molecules. “Today, things like that are standard,” says Leonhard Grill. “But it’s good training for students, who then learn how manipulations work and what the limits of such games are.”

So far, though, the small push with the tip has always made the molecules hop into their new position. The researchers never saw any rolling until Grill reinvented the wheel.

But how can physicists tell whether a molecule will hop or roll? And how can they prevent it from rolling off the shiny surface? Leonhard Grill grins: “The laws of physics that we know from everyday life don’t help us in the nanoworld. There are very different factors at play there.”

Take the wheel, for example: Once set in motion, a normal wheel just keeps rolling – assuming it doesn’t sink into the mud. Its mass and the associated inertia keep it moving. In the nanoworld, in contrast, masses are so small that gravity and inertia no longer have any influence. Instead, electrostatic and chemical forces take over.

Grill’s triptycene wheel, for example, is so strongly attracted by the slightly corrugated copper surface that it must be pushed forward continuously with the tip of the scanning tunneling microscope – similar to a finger rolling a six-sided pencil across a desk. And just like the finger, the tip of the microscope starts out behind the molecule wheel. While pushing, it invariably passes over the wheel to land in front of it – where the forced rolling then comes to an abrupt halt.

Such insights, however, are possible only when the tip can be positioned extremely precisely. There can’t be any attached monitor. The different colors represent the intensity of the measured current – and thus the contours of the surface. Even the untrained eye can recognize the individual atoms of the metal layer and the molecules lying on it.

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Such processes are reflected in the measured current intensity of the scanning tunneling microscope: when molecules hop to flee from the tip, the current first spikes, then suddenly drops, like a sawtooth. In contrast, when they roll, a wave motion is seen that matches very well with the wheel’s propeller form. “It was very exciting the first time we saw something like that,” recalls Grill. “And it also shows that, despite all of the playful elements, one can learn a lot about the physics behind the molecular building blocks if one looks very closely.”

Such insights, however, are possible only when the tip can be positioned extremely precisely. There can’t be any
away, the foundation of the 100-year-old building is massive, and the walls in the basement are a good meter thick.

ROLLING MOLECULES AS NANOWHEELBARROWS

Nevertheless, Grill and his team leave nothing to chance: when they take measurements, they turn off the light and the humming vacuum pumps. The room doesn’t even have air conditioning, as the airflow could cause the delicate stainless steel apparatus to vibrate.

“Evening is usually the best time to take measurements, when both the building and the staff have quieted down somewhat,” says Leonhard Grill. Then one can also reinvent the wheel.

But why do nanomachines need to roll in the first place? After all, the greatest advantage of macroscopic wheels – the significantly reduced frictional resistance – becomes far less important in the nanoworld. “A molecule with wheels can move in only two directions – forward and backward. Compared with an undirected diffusion, that would be a great step forward,” says Grill. Rolling molecules may also have the potential to surmount small steps on an atomic surface – one of the great obstacles to date in the spread of the tiny particles.

Furthermore, it is hoped that individual wheels are just the beginning. In the basement of the Kaiser Wilhelm Institute, Grill and his team have also examined molecular wheelbarrows – specially designed molecules that roll and that are intended to transport atoms one day. Even a nanotrain with several cars was already at the starting line. Unfortunately, the physicists couldn’t discern any rolling motion for either of the vehicles. The molecules were probably simply too strongly attached to the surface. "For us, this means that, together with the chemists, we must continue to tinker with the molecular design," says Leonhard Grill.

However, the Berlin-based researcher is interested in more than just mechanical problems. In Grill’s office, where the windows look out on Fritz Haber’s former villa, hang two covers...
Then – so the nanophysicists hope – molecular electronics will have its day in the sun. In any case, Grill and his team have already built the first wires. This undertaking was aided by molecules that chemists at Berlin’s Humboldt University custom designed especially for this purpose. The molecule designers used carbon compounds and blocked their reactive arms with weakly bound halogen atoms.

THE NANOWIRES ARE STILL VERY POOR CONDUCTORS

When heated in the scanning tunneling microscope, the halogen bonds broke open as desired. The molecular building blocks searched – entirely on their own – for new partners. They recognized reactive groups and formed stable carbon chains following the architecture the researchers specified. “With this form of self-organization, we are essentially imitating what nature has been doing very successfully for millions of years: it builds molecules with incredible precision and flawlessness,” says Leonhard Grill.

The autonomous molecular Legos result in wires that can be up to 100 nanometers long and extremely stable. The physicists noticed just how stable they can be when they played around a bit with the wires and pulled them across the surface. “That was incredibly easy, almost as if with a rope,” recalls Grill. “So we also tried to pull the wires up.” And indeed: using the tip of the scanning tunneling microscope, the researchers were able to raise their wires of the journal Nature Nanotechnology. The first one shows the molecular wheels, the other a couple of inconspicuous orange spots against a black background. They are nano-building-blocks that could one day change the computer world.

“In molecular electronics, it’s all about miniaturizing circuits down to the level of atoms,” explains Grill. Individual molecules are designed to form switches, wires, transistors and all the other necessary components, and to arrange in predefined architectures by self-organization – that is, without being directed by any external force. Researchers call this a bottom-up process. The tiny dimensions would mean short paths and thus extremely short computing times. The components would be cheap to produce, and would require extremely little electricity – after all, single electrons are already sufficient to trigger the desired functions. So far, however, the semiconductor industry is taking precisely the opposite route: it is trying to shrink its chips top-down by etching ever smaller structures into the semiconductors. Moore’s law, originally an empirical formula that states that the number of transistors on a computer chip doubles every 18 months, has long since become a target throughout the industry. But the miniaturization is slowly reaching its limits: transistors that are just a few atom layers thick can hardly be produced reliably with lithographic processes.
by 20 nanometers – and they didn’t break. This even gave them the opportunity to measure the current flow in the molecular wires for the first time.

In doing so, it became clear that, unlike in conventional wires, resistance increases exponentially with length – not necessarily a good sign for molecular electronics: “It still isn’t a wire in the traditional sense,” says Leonhard Grill, “as it’s a very poor conductor. But at least we were able to show that electrons can be transported across such constructs.”

The first ideas for nanocircuits are also already on the table. And once again, nature is the role model: In the eye, for example, there are two variants of the retinal molecule, called isomers. When light hits the retina, the one form changes into the other, the nerve cells receive an impulse, and the brain is notified.

That is exactly what the physicists in Berlin have realized on surfaces: They use light or heat to start the isomerization. They use it to refer to a process in which molecules to independently grow into larger structures due to natural physical or chemical forces.

Alternatively, the scanning tunneling microscope itself can be used as the trigger: although very little electricity flows between the tip and the sample molecule, on the nanoscale, a few electrons are sufficient to produce a high current density that is great enough to trigger the isomerization and thus activate the molecular circuit.

“The next major goal now is to couple the various systems – for example a circuit with a wire,” says Leonhard Grill. And then? Will the molecules later automatically join together to form a tremendously powerful and simultaneously efficient supercomputer?

**USING THE LEGO PRINCIPLE: LEARNING BY BUILDING**

Leonhard Grill, the realist, shakes his head. “I can’t imagine that we can get a complete chip with its millions of molecules to independently grow into a highly complex architecture.” If molecular electronics should one day actually prove itself, then most probably in combination with the current chip technologies. But then new and maybe even revolutionary applications may be possible – for example in sensor technology.

And the nanocars that have long been driving across the screen in every science-fiction B-movie already? Grill laughs. “It’s really difficult to predict applications, especially in a field such as nanoscience, in which completely new effects occur.” After all, thousands of years ago, when the wheel was first invented, no one had ever thought about the balance spring of watches or the drive train of electric cars, either.

So it’s very possible that nanomachines will one day clean surfaces, transport molecules or build simple structures – but Grill and his team are focusing on other things. These researchers follow the Lego principle: No one can say exactly what the end result will be when all components have been mounted. What matters is that the building process brings new insights.

“In any case, we aren’t doing this because we would like to have a molecular chip or a nanocar in 30 years,” says the 40-year-old, and looks out the window. “We do this because we find it interesting, because we want to understand what happens. But most of all, we do it because we are curious.”

**GLOSSARY**

**Scanning tunneling microscope**
A very fine, electrically conductive tip scans a likewise electrically conductive sample surface. Since the tip does not touch the sample, electrons tunnel from the sample to the tip. The tunneling current that flows in this process is strongly dependent on the distance between the sample and the tip. This makes it possible to determine the surface structure.

**Bottom-up**
Materials scientists borrowed this term from the field of software development. They use it to refer to a process in which small construction units combine to form larger structures due to natural physical or chemical forces.

**Top-down**
The reverse of the bottom-up principle: smaller structures are developed from a larger system, such as a silicon wafer.

**Retinal**
Together with the protein opsin, this forms the rhodopsin of the retina. Light changes the structure of retinal, causing opsin to be split off again and triggering a signal cascade that results in a nerve impulse to the brain.

**Isomerization**
When a molecule changes its structure in that its atoms relocate, without atoms being taken up or released.
Microbes in a Dissolved Environment
The subject of our research is in here,” says Thorsten Dittmar, pointing to the table in front of him. On it stands a glass volumetric flask filled almost to the brim with water. Dittmar’s office on the University of Oldenburg campus is flooded with light, yet the container appears to hold nothing but ordinary water. Slightly cloudy perhaps, but that’s all. “Exactly one liter of North Sea water, full of single-celled organisms,” he continues, “around a billion in total. A few algae, but mainly bacteria.” In other words, there are as many single-celled organisms living in just seven liters of seawater as there are people on Earth.

But Thorsten Dittmar is less interested in all the microorganisms in his volumetric flask than in what they eat – or rather don’t eat: dissolved organic material, all varieties of water-soluble carbon-containing molecules. A milligram of this material, no more than one grain of powdered coffee, is swimming around invisibly in the flask. That doesn’t sound like much, but if we extrapolate the carbon bound in it to the total volume of all the world’s oceans, it comes to an unimaginable 700 billion tons. This is the total amount of carbon contained in all the world’s living organisms.

The main source of dissolved organic material is the photosynthesizing plankton in the sea – algae and bacteria that, as they grow, continuously deposit metabolic products into the water. These molecules are also released when plant plankton is eaten by animal plankton or destroyed by viruses. In turn, this dissolved material forms the diet of bacteria, which must get by without photosynthesis.

As the dissolved organic substances float in the sea, they are transformed in various ways by largely unknown processes, resulting in an almost infinite diversity. Dittmar estimates that there are between ten million and a hundred million different organic substances drifting in the ocean. “Only about 5 percent of this material can be assigned to known chemical structures, such as amino acids, sugars, fats and a few others. The remaining 95 percent are completely unknown,” he explains.

Accordingly, in September 2008, the scientist began setting up a new and unusual junior research group at the Max Planck Institute for Marine Microbiology in Bremen. Unusual not only because it would be working in an almost unknown area of research, but also because of its location: at the Carl von Ossietzky University in Oldenburg, an hour’s drive from Bremen.

This is a unique model for the Max Planck Society, none of whose other working groups are based completely outside the parent institute. The advantages of the Oldenburg model work both ways: the microbiology-oriented Max Planck Institute in Bremen benefits from...
We’re the Max Planck Institute’s nutritionists so to speak.

the long geochemistry tradition of the Institute for Chemistry and Biology of the Marine Environment at Oldenburg University, which in turn can complement its own microbiology research with that of the institute in Bremen. Dittmar’s working group itself, as a know-how interface, benefits doubly.

“I feel really at home in Oldenburg,” says Thorsten Dittmar, who most recently conducted research in the US at Florida State University in Tallahassee. No wonder, since the Marine Geochemistry working group, of which he was originally the sole member, has now grown to 16 employees in less than three years. This is a clear indication of the scale of the need for research in this field.

The working group focuses on three main questions: What parts of the dissolved organic material do marine microorganisms eat? What do they not eat, and why not? How do the microorganisms’ preferences affect the climate? “We are the Max Planck Institute’s nutritionists, so to speak,” says the scientist with a wink.

To answer these questions, we first have to know what is actually on the menu. The researchers are thus trying to pinpoint the identity of the many unknown substances – a monumental task. First they have to obtain the material for analysis, through investigations in every corner of the world – the Gulf of Mexico, the polar seas of the Arctic and Antarctic, deep-sea hydrothermal vents and right on their own doorstep in the North Sea off Helgoland.

The scientists make regular trips on the Polarstern, a research ship undertaking scientific expeditions commissioned by the Federal Republic of Germany and operated by the Alfred Wegener Institute in Bremerhaven. The water samples the researchers obtain from different depths are filtered on board to remove the microorganisms and other suspended material, and then desalinated. Absorber cartridges are used to bind the organic components, which finally reach the laboratory as a yellowish, highly concentrated solution.

“Instead of 10 liters per water sample, we come home with only 10 milliliters. That saves a lot of room,” says Dittmar. What follows in the laboratory in Oldenburg is one of the biggest challenges of all for an analytical chemist. For conventional molecular analysis, the individual components have to be separated from one another – an impossible task given the diversity of the dissolved organic compounds and their sheer number of over ten million different molecules.

**ANALYSIS USING THE STRONGEST MAGNETS**

Fortunately, Dittmar’s laboratory houses a revolutionary instrument that costs more than two million euros and weighs four tons. Behind a transparent soundproof wall stands Germany’s most powerful mass spectrometer, acquired in September 2010. “This piece of equipment is unique in marine research. We can use it to measure the mass of a molecule with a precision of less than the mass of an electron,” Dittmar says with pride. There are only five of these systems in the world, and only the one in Oldenburg is used for marine research. The core of the system, which resembles a gas tank and is as tall as a human, is currently the world’s strongest commercially available magnet used in mass spectrometry. And as luck would have it, the only company that sells these systems is essentially around the corner – in Bremen.

Ultrahigh resolution mass spectrometry has made what may well be the crucial breakthrough in research into dissolved organic material. This new technology measures so accurately that scientists can determine the precise chemical formula of each molecule. It also shows what elements make up a molecule and how many there are. Only with this new apparatus was the enormous variety of molecules in the oceans revealed. Some 5,000 to 10,000 different chemical formulas can be ascertained in a sample within half an hour. Using this method, the researchers have identified several tens of thousands in total.

But why don’t bacteria simply eat their enormous pantry bare? Most dissolved organic material has been drifting around in bite-sized pieces in the deep sea for many thousands of years without a bacterium taking the bait. “Picture it as a non-stop Oktoberfest in the ocean, with a few grilled chickens being snapped up, but no one touching the beer,” says Thorsten Dittmar.

But the scientists have solved at least one part of the puzzle. For the first time, they discovered a new and unexpected class of substances – functionalized polycyclic aromatic compounds. No previous knowledge existed of any organism that could produce these hydrocarbons, which consist of several carbon rings. They occur only when an organic substance burns or is heated by geothermal energy in deep sediment layers.

The research team found increased concentrations of these substances especially in very old deep water, which was last at the surface long before the beginning of industrialization. This rules them out as a source of manmade combustion processes, as most manmade substances that move from land to sea are broken down on the surface by sunlight.

The aromatic compounds that Dittmar and his colleagues have found evidence of everywhere in the deep sea may come from the sediments on the ocean floor. Dittmar suggests the following scenario: seawater that makes a sort of extra pass through the seabed...
Penguins are constant companions on Polarstern expeditions (bottom), and stormy weather is also a routine event for the scientists (left). The scientists use a CTD rosette to collect water samples from varying depths (right).
appears again at, for example, hydrothermal sources with temperatures of more than 400 degrees Celsius. In this way, organic materials are presumably released from the sediments and washed, chemically altered, into the deep sea. Since destructive sunlight is not present here, they remain stable for a long time. “Up to 20 percent of dissolved organic material could be transformed in this way through the action of heat,” estimates Dittmar.

Thorsten Dittmar opens the injection unit of the mass spectrometer. From the syringe at the right edge of the photo, the probe penetrates through the red sheathed capillary into the injection source.

This would also explain why bacteria leave most of the dissolved organic substances in seawater alone – perhaps they simply don’t have suitable tools for breaking down the altered substances, forcing them to do without many originally tasty morsels.

We can really only be thankful for this involuntary diet of the bacteria. If also the stable part of the dissolved organic material were eaten, releasing the carbon bound within, the atmosphere’s carbon dioxide content would easily double – with correspondingly disastrous consequences for the climate. However, the reverse scenario is also conceivable: if the bacteria were to suddenly reject part of their food, dissolved organic material in the ocean would build up at the expense of atmospheric carbon dioxide. An increase in dissolved organic material from the current 1 milligram to 1.5 milligrams per liter would halve the atmospheric carbon dioxide content and reduce it to the levels of the last ice age – producing a rather cool breeze in the process.

Bacteria may have triggered an increase in carbon dioxide in the atmosphere once before, 600 million years ago. At that time, the Earth was like a giant snowball: the global average temperature was well below the current figure, and the oceans were largely frozen. One theory (not without its detractors) suggests that more oxygen found its way into the oceans, enabling bacteria to break down dissolved organic material. The carbon dioxide released as a result escaped into the atmosphere and triggered a greenhouse effect.

Whatever the effect of global warming at that time, the eating habits of bacteria in the sea have the potential to influence the climate. No wonder, then, that scientists have recently begun talking about dissolved organic material in connection with geoengineering – manipulating natural cycles in order to counteract climate change (MaxPlanckResearch 3/2010, page 36 ff.).

INTERFERING WITH NATURAL CYCLES CAN BE DANGEROUS

According to the theory, if the bacteria could be induced to ignore part of their food, the carbon dioxide levels in the atmosphere would fall and the greenhouse effect would be reduced. But Thorsten Dittmar is skeptical: “Before we start manipulating natural processes, we first need to understand every last detail. Without that knowledge, we won’t come anywhere close to estimating the impact of such interference.”
Oldenburg is home to Germany’s most powerful mass spectrometer.

However, the reservoir of dissolved organic substances is already changing, even without geoengineering. Global warming is slowly melting the permafrost layers in the Siberian and Canadian tundra. This releases greater quantities of organic material, which is washed down the many rivers and into the North Atlantic. The intriguing question now is: what happens to this additional input of dissolved organic substances? Is it eaten, which would be bad for the climate, or does it remain stable and end up in the deep sea?

In order to discover what becomes of the additional dissolved organic material, the researchers must not only find out what bacteria leave on their plates, but also identify their favorite dishes. Thorsten Dittmar and his colleagues are currently analyzing water samples from the Helgoland long-term series: since 1962, researchers have been continuously measuring salt content, temperature and the species composition of plant, animal and bacterial plankton off the island. This is done once a week, always at the same location.

By comparing the Helgoland data on algae and bacteria density with the newly acquired information on the composition of dissolved organic material, the scientists have identified important key substances. When a certain single-cell diatom blooms, it produces, among other things, an organic substance that needs a bacterium in order to grow. “The organic substances are thus part of countless numbers of specific connection networks between the microorganisms in the sea,” says Dittmar.

This allows dissolved organic material to be examined in waters where the living conditions for bacteria differ. These living conditions, such as water temperature, affect the composition and activity of bacterial communities, and thus the composition of dissolved organic material. In this way, the research can contribute to a better understanding of global materials cycles and possible alterations caused by climate change.

A brief glance at the most recent assessment report by the World Climate Council (IPCC) reveals the importance of the work being done by the Max Planck research group in Oldenburg. Published in 2007, its findings on climate change form the main basis for political decisions on climate protection. However, it is futile to search for any reference to dissolved organic material in the report, with runs to more than one hundred pages. Knowledge levels in 2007 were still far too patchy for meaningful integration of the 700 billion tons of carbon into global climate models. “Now it’s time for an update,” says Thorsten Dittmar.

GLOSSARY

**Organic molecules**
Most carbon-containing compounds are known as organic compounds. After hydrogen, the element that can form the largest number of chemical compounds with other elements is carbon. For example, carbon can form chains and rings with itself and other elements through single or double bonds. That is why carbon compounds are considered to be the basis of all life on Earth.

**Functionalized polycyclic aromatic compounds**
Polycyclic aromatic compounds are organic molecules in which atoms are arranged in several rings. The binding electrons of the ring structures are not assigned to a single bond, which means that the molecules are highly inert and stable. Functionalized aromatic compounds further possess additional molecular residues, such as hydroxyl or amino groups, which increase the polarity of the compounds and thus their solubility in water.
Debating the Japanese Approach to Dispute Resolution

The Japanese are far less likely to settle their disputes in a court of law than Europeans or Americans. Is this a product of their mentality? Do they know of better ways of resolving conflict? Or are they lacking in legal alternatives? These are some of the questions being explored by Harald Baum and his colleagues in the Japan Unit at the Max Planck Institute for Comparative and International Private Law in Hamburg.
Let there be eternal peace and friendship between His Majesty the King of Prussia and His Majesty the Taikun of Japan, their heirs and successors...”

The agreement reached 150 years ago between the Prussian envoy Friedrich zu Eulenburg and his Japanese host, and enshrined on January 24, 1861 in the German-Japanese Treaty of Amity, Commerce and Navigation, laid the foundation for a bilateral relationship that has borne many fruits – not least among them an enthusiastic following in Japanese society for “Baumkuchen” (tree cake) and other classics of German culture. Conversely, there are few households in Germany that do not own goods imported from Japan.

For a long time, Japan was Germany’s most important economic and trade partner by far in the Asian region. It has since come to share this role with China. Despite this fact, experts lament a lack of interest in the old friend across the seas. “Especially our knowledge of Japanese law, in Europe at least, is still not commensurate with the country’s sustained economic and political importance,” says Harald Baum, a legal expert and founding editor of the Journal of Japanese Law at the Max Planck Institute for Comparative and International Private Law in Hamburg. Under his leadership, scientists in the Japan Unit are studying, documenting and analyzing the diverse origins and development of the Japanese legal system in order to close this gap in our knowledge.

THE GERMAN CIVIL CODE AS A MODEL

For the scientists in Hamburg, whose primary focus is on a comparative study of the law, the country offers exciting insights into how norms that originated in the West are applied in a different culture and social system. As Professor Baum points out, déjà vu is a common feeling among legal experts studying Japanese law. Among the examples he cites are civil law, which mirrors many aspects of its German counterpart, and financial market law, which includes many familiar features of the US legal
system. In fact, many of the seemingly familiar sections of Japanese law derive from the adoption of Western law, a process that, according to legal historians, took place in two main thrusts.

The first of these came at the end of the 19th century, during the time of the Meiji Restoration. The then new government was convinced that a new legal system was required in order to efficiently modernize the economy, and it looked to the West for inspiration and reform. French, English and above all German law provided the model they sought. “In the space of just three decades they established a new, fully functional legal system with all of its attendant institutions,” says Harald Baum, describing the impressive pace at which the Japanese reformers progressed. “It was a major cultural achievement that has yet to be equaled.”

The fact that German legal experts in particular find many familiar passages in Japanese civil law is something Baum attributes to the work of two reform commissions that formulated the new laws on the government’s behalf and took as their model the German groundwork for the Civil Code. The reformers chose to give preference to German law rather than its French counterpart, on which the reform process had initially been focused. In Harald Baum’s opinion, there were not only political, but also technical reasons for their choice. “Back then, the German Civil Code that was just emerging was considered to be more modern than the French Civil Code, which was almost a hundred years older.”

LEGAL IMPORTS IN A DIFFERENT CULTURAL ENVIRONMENT

The numerous elements of US law, in contrast, were not imported until much later. This second great reception of Western law in Japanese history was, however, rather less voluntary. In the process of “democratizing” the Japanese economy after World War II, the Allies broke up the huge family-owned industrial concerns, implemented a land reform, created a new constitution and refashioned large parts of the country’s commercial law. “All of this took place under strong American influence, and often directly mirrored the laws of the United States, which, in some cases, were adopted word for word,” explains Professor Baum.

By its very nature, the resulting amalgam of legal systems makes Japanese law an attractive field for scientists such as Harald Baum and his colleagues in Hamburg to conduct their comparative studies in. Their work is by no means redundant simply because many sections of German and Japanese law coincide. “We must not forget that these familiar features of modern Japanese law are imports that are being applied in a cultural, socio-political and social environment and value system that differ markedly in their traditions from those of the countries of origin,” Baum emphasizes.

Nevertheless, proponents of his discipline are still faced with the question of how to approach a comparative study of Japanese law in a manner that will provide a meaningful interpretation of the legal reality in the world’s fourth-largest island nation. For a long time now, there has been a lively debate among international experts over the fundamental methods by which future legal comparisons should be drawn. “It’s a question of whether, over and beyond traditional functional comparisons, it is also necessary to compare legal cultures,” explains Baum.

Comparisons can be made to serve variously accentuated goals. On the one hand, in legal practice, when a German court decides a case, it is frequent-ly necessary to consider how a specific social problem, circumstance or situation is dealt with under a foreign legal system – for example when it comes to ruling on maintenance payments for the children of a divorced couple, one of whom is a foreign national living abroad. Often, particularly in the Euro-
pean legal area, lawyers find the same or similar solutions as those that apply in their own domestic law. In this functional approach, a comparison is generally directed at the common features of the systems in question.

However, a comparative study of a foreign legal system can go further than this to facilitate a fundamental understanding of another legal culture. In this case, the rules of law are considered as a condensed version of the culture in question, and the legal system as a social subsystem that cannot be studied in isolation from its social environment. Taking this view of a foreign legal system, it is more likely to be the differences that take center stage.

“Bearing in mind that the traditions of Japanese law are fundamentally of non-European origin, it is preferable, in my opinion, to broaden one’s perspective to include the cultural and institutional context,” says Harald Baum. After all, the members of the Japanese reform commission at the end of the 19th century did not simply copy Europe’s legal templates and translate them. Instead, they used a broad comparison of legal systems as a basis and integrated elements of differing systems into newly drafted codes of law that took traditional values into account. The researcher cites the motto of the Meiji government’s legal reformers: “Wakon yōsai – Japanese spirit, Western knowledge.”

Together with his colleague Moritz Bälz, Professor of Law at Frankfurt University and co-editor of the Journal of Japanese Law, he recently edited a comprehensive reference book of Japanese commercial and economic law. The two scientists devoted an entire chapter to a two-fold consideration of legal realities from two perspectives.

THE JAPANESE RARELY GO TO COURT

On the one hand, there is the question of how the Japanese conduct themselves in cases of dispute. Their behavior differs from that of most Europeans and Americans insofar as the Japanese are far less likely to take disputes to court. Legal experts use the term “litigation density”: there is a far lower density of litigation in Japan in terms of both disputes between citizens and conflicts between citizens and corporate enterprise. “The courts hand down far fewer business-related judgments than in Germany and, above all, in the US,” explains Baum.

This is where the second perspective from which Baum and his colleagues view Japanese legal reality becomes important: the issue of how the law is implemented in the relationship between the state and corporate enterprise in matters of business, such as the admission of new financial products. At least until a few years ago, this field was mainly the preserve of bureaucrats whose influence and scope were and still are considerable.

“Anyone who wants to export to Japan or set up or take over a business there should have a clear understanding of the role and importance of bureaucrats and their ability to influence the proposed project,” the expert stresses. At least until fairly recently, Japanese business affairs have been conducted not so much under the guidance of the country’s laws as at the discretion of its administrators. “The process is predominantly informal and, as such, lacks transparency, and is rarely subject to legal jurisdiction,” says Baum.

To this day, this informal application of the law is often decisive in current practice, even if it does not take place on quite the same scale as before. Sometimes it takes the form of written decrees, but usually it is a matter of verbally communicated “suggestions.” These are not of any legally binding nature, but are nevertheless complied with for fear of sanctions of some other kind. It may be that permits will be denied in other matters, or that transactions become mired in other bureaucratic impediments.
“This form of ex-ante regulation has, however, been cautiously replaced for some years now by the ex-post control of market behavior by the courts,” observes Harald Baum. In the latter case, access to the courts and the efficiency with which justice is served play a special role. For this reason, the major process of judicial reform that began in Japan a few years ago is essentially aimed at drastically increasing the number of legal practitioners.

Impetus for the reforms was provided by the sustained structurally induced economic crisis that has afflicted Japan since the early 1990s. The close interaction between bureaucracy and business that had long functioned successfully was no longer effective in the open market conditions engendered by a globalized economy. The valiant reform of this regulatory model was intended to help Japan overcome its economic crisis.

WHY ARE CONFLICTS OFTEN RESOLVED OUT OF THE COURTS?

In the private sphere, the Japanese still rarely resort to the courts. Even though the Civil Code has made provision for them to do so for 100 years now, it scarcely occurs to them to go to court over the height of their neighbor’s fence – a not uncommon occurrence here in Germany.

Just why the Japanese evidently prefer to settle private conflicts out of court has long provided legal experts with food for thought – and for argument. “A sometimes quite intensive debate has been raging for over 40 years,” says Harald Baum. It was triggered, he adds, by a paper published by the legal sociologist Takeyoshi Kawashima in the 1960s. His relatively short exposition on “Dispute Resolution in Contemporary Japan” has influenced practically

“We should stand by our programs as far as possible”

Earthquake, tsunami, nuclear meltdown – the catastrophic events in Japan had a deep impact on Harald Baum and his colleagues at the Max Planck Institute for Comparative and International Private Law, not least because many of the staff in the Japan Unit feel not just a professional but also a personal bond with the country.

Mr. Baum, there were a variety of festivities and events planned for this spring to celebrate the 150th anniversary of the official treaty of friendship between Germany and Japan, some of which were due to take place under the auspices of your department – what will happen now?

Harald Baum: All of us who are deeply involved with Japan and know and appreciate the country are of course particularly affected by the tragic events that have taken place. Our thoughts are with our many friends and colleagues and their families who live there. I have been impressed by the disciplined manner in which the Japanese are dealing with the after-effects of the disaster. Under these circumstances, it is indeed difficult to celebrate and proceed with the symposia we were preparing this year in Germany and in Japan to mark “150 years of friendship Japan-Germany.” On the other hand, our Japanese friends have asked us to stand by these programs as far as possible, to demonstrate that life, including academic life, goes on. From this perspective, the various joint events, which focus on aspects of law, would seem to offer an opportunity for us to express our sustained commitment to the country and its people. With this in mind, all of the events in Germany, at least, will be held as planned.

Have there been any program changes?

Yes, there was a three-day comparative law symposium set to be held in Tokyo in mid-April with the participation of the German Ministry of Justice and other organizations. It was intended as an academic centerpiece in Japan, but after careful consideration, and in consultation with our Japanese partners who co-organized the event, and not least on their recommendation, it has been postponed until the fall.

To what extent were your partners in Japan directly affected by the disaster?

We have since been able to make contact with all of our Japanese colleagues with whom we regularly cooperate. Fortunately, they and their families are all doing as well as can be expected under the circumstances. While the same might not, perhaps, be said for colleagues working in the natural sciences with large-scale equipment that is dependent on energy supplies, no concerns have reached us from our fellow legal researchers about projects that have been interrupted and cannot currently be continued.
How is your joint work proceeding?
Once the initial shock wore off, our work essentially continued with the usual professionalism. This, too, reflects the impressive discipline displayed by our Japanese partners, from whom we have not heard a word of complaint.

What aid and support can you offer your Japanese colleagues? Are there any concrete projects?
Of course we are all concerned with how best to help. At the institute, we suggested to our Japanese colleagues who work here that they should extend their stay. However, without exception, they politely declined, citing the duties they must attend to in Japan. Likewise, the offer to switch the symposium I mentioned earlier to Germany in order to relieve some of the burden on our colleagues in Japan was noted with due thanks, but nevertheless declined. Various German-Japanese organizations, among them the German-Japanese Association of Jurists, have set up accounts to enable their members to make donations as a means of offering at least some support for the traumatized victims at the heart of the devastation who have lost everything.

Interview: Birgit Fenzel

CULTURE & SOCIETY

Private Law

every Western publication on the nature of Japanese law that has appeared since, even if the majority of authors are united in rejecting his theses.

In Baum’s opinion, Kawashima was essentially advocating a cultural explanation. “In his view, for reasons of tradition, the Japanese have a less conflict-oriented awareness of the law and they don’t define their actions and relationships in the form of enforceable legal positions in the same way that Europeans or Americans do.” According to Kawashima, their behavior is prompted instead by the need to find a balance of interests and preserve social peace.

His theory reflects the sense of right and wrong that prevailed in Japan under the Tokugawa regime – a feudalist era of Confucianism in which the law was considered to be decreed and implemented solely by the state. “Private disputes were regarded as moral flaws with which the government concerned itself only in exceptional cases,” explains Baum, describing the legal mentality that prevailed into the mid-19th century.

Against this background, Kawashima regarded the reluctance of his fellow countrymen to resort to the courts as “pre-modern.” However, he anticipated that, as Japan became a more modern and international society, its appreciation of the law would change accordingly.

Other legal experts, on the other hand, attribute the national reluctance to litigate to the Japanese judicial system itself. Chief among them is the American specialist in Japanese law John Owen Haley, who voiced his criticism of Kawashima’s cultural approach as early as 1978. “In an article that has since acquired classic status, he provocatively rejected Kawashima’s theses as pure myth,” says Harald Baum.

In place of the vague concept of a legal mentality derived from tradition,
Haley points to specific institutional impediments that prevent the Japanese from enforcing their rights through litigation. In Haley’s interpretation, the tradition of seeking consensus rather than going to court developed, not of its own accord, but as a result of skilled socio-political management.

TOO GREAT A BURDEN ON THE COURTS

On the one hand, until the legal education reforms a few years ago, the number of licensed attorneys and judges was kept artificially low by the fact that only very few applicants were admitted to the central judicial training institute. All young jurists in Japan who wish to work as judges, prosecutors or attorneys are required to undergo training at this institute in Tokyo following their university education, as in Germany.

For decades, the pass rate in the entrance examination was less than 3 percent of each year’s applicant cohort,” explains Baum. As a result, the population is, to this day, massively underprovided with lawyers in many areas of Japan and especially in the provincial prefectures, severely impeding their access to the courts. The fact that the courts work very slowly because they are overloaded serves as a further deterrent to potential litigants. It is also very expensive to hire a lawyer.

Haley’s theories as to why the Japanese shy away from litigation, despite being shared by various other Japanese legal sociologists, were initially disputed. However, 20 years after they were first published, they were officially confirmed by a representative survey commissioned by the Japanese government in cooperation with the Japanese Federation of Bar Associations and the Japanese Supreme Court. Just 18.6 percent of those interviewed were content with the way the civil justice system in Japan worked, and only 22.4 percent regarded the system as sufficiently accessible. The main reasons cited for this general dissatisfaction were the high costs of litigation and the excessive time required for cases to be heard.

THE NUMBER OF ATTORNEYS IS PRESCRIBED

Harald Baum considers a third explanation for the relative lack of litigation to be interesting, if not entirely accurate: the reluctance to go to court has also been claimed as proof, not of the weakness, but of the strengths of the Japanese justice system. The institutions designed to find extrajudicial solutions to conflicts render much litigation superfluous. The parties, it is claimed, are thus able to resolve a dispute faster and at lesser cost. What’s more, the end result is often the same as that of going to court, says Harald Baum. “For that reason, in some, but not all, areas of the law, the avoidance of litigation is simply a rational economic alternative rather than the expression of a specific legal mentality.”

For Harald Baum, the explanation for the comparatively low litigation density lies somewhere between these three positions. He is convinced that institutional and cultural factors interact with one another in a dialectical process, or at least serve to complement one another. Whether he is correct in this assessment will be revealed when the practical reforms of Japan’s legal training system bear fruit. The number of successful candidates passing the en

Compared with the citizens of other industrialized countries, the Japanese rarely turn to the courts to resolve their conflicts. This is confirmed by the above graph showing the density of civil litigation in selected countries, as well as a breakdown of the types of cases. Why there were more disputes settled in Japanese courts in 1883 than in 1990 is one of the questions Harald Baum and his colleagues would like to answer.
Comparative law
The study of the legal systems of differing countries. This usually takes the form of a so-called functional comparison, which investigates how a given social problem is resolved in other systems of law. The process concentrates mainly on the common features of legal solutions. Alternatively, from another perspective, researchers may focus on the differences in how norms are implemented in other legal systems. In this case, there is typically a greater emphasis on anthropological, cultural and other institutional aspects.

GLOSSARY

Ex-ante and ex-post regulation
These terms describe two differing regulatory strategies. In the first case, access to the market by future participants and/or the introduction of new products are controlled in advance (ex-ante) by the state, which demands qualifications of both a professional and a personal nature. In the second case, market participants are controlled retrospectively (ex-post) by the courts when civil suits arise.

Meiji Restoration
1868 was a year of upheaval in Japan and marked the beginning of modernization as the country was opened up. The shogunate regime that had governed the country for nearly three centuries and kept it hermetically sealed off from the outside world was disposed of by reformers who restored the Emperor (Tennō) to all positions of power – thus "Restoration." The economy, society and justice system were all comprehensively reformed.

Entrance examination for legal internships has already risen from fewer than 1,000 per year to more than 2,000. The target is to reach 3,000 interns per year.

"It’s worth noting, however, that despite the fundamental change they are aiming for in the resolution of conflict, the authors of these judicial reforms still have no faith in the market for legal services," adds Baum. Instead of, as in other industrial countries, allowing the market to determine the rise or fall in the number of licensed attorneys, they continue to set fixed targets.

For Harald Baum and his colleagues researching in the field of comparative law, the question now is whether the reforms that have been introduced since 2000 will usher in Kawashima’s expected era of legal modernity. They are aimed at simplifying access to justice, making the litigation process more efficient and stimulating a culture of constructive argument. “It is likely to be too soon yet to reliably estimate whether the goals of the reforms have been achieved and whether any sustained changes have occurred in the Japanese attitude to litigation,” Baum warns. “Social change, especially where it affects institutions, takes place very slowly, and often in unforeseeable ways.”
Life is chemical fluctuation – this is the view that shaped the research of Munich-born biochemist Feodor Lynen, who would have celebrated his 100th birthday this year. In clarifying the structure of "activated acetic acid," he laid the foundations for understanding the many processes of formation and breakdown in the cell, and for the study of such diseases as diabetes and arteriosclerosis. Lynen, a Director at the Max Planck Institute for Cellular Chemistry, was awarded the Nobel Prize in 1964 for his work on cholesterol and fatty acid metabolism.

The Great Experimenter

The article that appeared in the journal Angewandte Chemie in 1951 was short and to the point, not more than a page long. The molecule it described, in contrast, was so complex that scientists had spent years puzzling over what it might look like. The author, Feodor Lynen, had finally done it: he had put the pieces of the jigsaw together in the right combination to reveal the structure of acetyl coenzyme A, otherwise known as activated acetic acid – a compound that plays a key role in cell metabolism.

Feodor Felix Konrad Lynen was born in Munich's Schwabing district on April 6, 1911, the seventh child of a professor of mechanical engineering. Affectionately known as "Fitzi," he showed an active interest in chemistry from an early age, carrying out experiments in the attic of his parents' villa. After "making holes in his Sunday best trousers and an explosion resulting in slight injuries to his face and hands," he put his experiments temporarily on hold until he began to study chemistry at Munich University in 1930.

In the early 1930s, Munich was a stronghold of organic chemistry. Famous names such as Justus von Liebig, Adolf von Baeyer and Richard Willstätter had taught and conducted their research there. The range of topics was broad; scientists studied not only the structure of natural substances, but also the chemical conversions that took place within living cells. In the lab of the man who would be his father-in-law, Heinrich Wieland, the 1927 Nobel laureate, Lynen did his Ph.D. "On the Toxic Substances in Amanita" before turning his attention to a more digestible subject – brewer's yeast (Saccharomyces cerevisiae), which he procured from Munich's Löwenbräu brewery.

Using radioactively marked compounds, Heinrich Wieland investigated the metabolic processes in the yeast. This easy-to-handle model organism is eminently suitable for clarifying biochemical questions. Wieland was particularly interested in the fate of acetic acid, a very simple organic molecule consisting of just two carbon atoms: a methyl group (CH₃) and a carboxyl group (CO₂H).

As the scientists of the day already knew, acetic acid plays a central role in metabolism: it is produced when carbohydrates, fats and proteins are burned, and is also a component of various biomolecules, such as vitamins, cholesterol and hormones. What they did not know was how the chemical reactions occurred, given that acetic acid is, by nature, slow to react. It must first be activated – and that was the crux of the matter – before it will convert anything at all.

Lynen, too, became captivated by "activated acetic acid" since, in his view, "the processes of life [offer] the most fascinating problems for a chemist." And so his interest turned initially to converting acetic acid into citric acid – the reaction at the center of the aerobic breakdown of carbohydrates.

Heinrich Wieland had made an interesting observation in this respect: he shook yeast cells together with oxygen for many hours, which used up all the usable (oxidizable) substances. If acetic acid was then added to "depleted" yeast of this kind, only after several hours could it be oxidized and thus used to produce energy.

But what exactly happened inside the reaction vessels? Feodor Lynen initially postulated that the acetic acid got its energy boost through phosphorylation – the addition of a phosphate group. Yet his experiments with acetic acid and inorganic phosphate ended in disappointment every time: the reaction mixture contained not a drop of citric acid.
Many years went by before this problem was resolved. The initial spark came from a discovery made by biochemist Franz Lipmann, who was working in the US. He had isolated a previously unknown coenzyme from pigeon-liver extract in 1947. Since it was capable of transferring acetyl groups (the remains of acetic acid), he named it coenzyme A. It contained pantothenic acid, adenosine, phosphate and sulfur, and was directly involved in acetylation reactions – an indication that the acetylated form of this coenzyme may conceal the portentous “activated acetic acid.” However, the structure of the compound was so complicated that it was not apparent how the acetyl was bound to the coenzyme.

The memorable moment when he discovered the answer was later described by Lynen in the following terms: “My brother-in-law, Theodor Wieland, was spending the holidays at his parents’ house, which is next door to our house. He had been [...] working on pantothenic acid, the vitamin that Lipmann had recognized as a component of coenzyme A. We spent the whole night discussing how acetate and pantothanic acid could be bound to each other, but we did not reach a solution. On my short walk back to our garden it occurred to me that the residual acetate may be bound, not to the pantothenic acid, but to the sulfur.”

Experiments with acetyl coenzyme A from the boiled extract of yeast proved Lynen right. Within two months he had confirmed his presumption experimentally, and then he immediately put his findings down on paper. But he had a nail-biting wait until they were published in Angewandte Chemie. “It all seemed so simple to me now, I could hardly believe that no one would have the same idea in the intervening period,” reported Lynen.

At the time, numerous research groups were working on the problem of “activated acetic acid.” Would someone beat him to it at the last minute? In the end, what followed was the news that his “discovery had hit the biochemists in the US like a bomb.” The publication had struck Fritz Lipmann “without warning”.

His clarification of the structure of “activated acetic acid” brought Feodor Lynen international recognition. From then on, his career took a steep upward trajectory. In 1953 he was appointed the first professor of biochemistry at a German university. The following year he assumed the directorship of the Institute of Cellular Chemistry that had been specially established for him within the Max Planck Society. The institute later merged with the Max Planck Institute of Biochemistry in Martinsried, near Munich. In 1964, Feodor Lynen won the Nobel Prize, together with Konrad Bloch, for his discovery of the “mechanism and regulation of the metabolism of cholesterol and fatty acids.”

“I am happy in my job, but I have never let it become an obsession. I have always taken the time to enjoy life,” said Lynen of himself. He demanded absolute top performance from his people, as he did from himself, but working with him also promised a measure of fun away from the lab bench. In the collection of essays entitled Die aktivierte Essigsäure und ihre Folgen (“activated acetic acid and its consequences”) that was published to mark his 65th birthday, former members of his team wrote contributions on the subject of “Feodor Lynen and I.”

The contributions tell of relentless lab work, often late into the night, and Lynen’s dreaded visits to the lab to keep up to speed on the latest findings – or lack of them: “You great lump!”, “Well, you great artist?”, “You can throw that right away!” – the boss’s comments “caused people to go either ashen white or beet red in the face, depending on their temperament.”

But they also recall the ski trips and hiking expeditions they all took in the Alps, the Mardi Gras holidays, the garden parties in Starnberg and sociable gatherings at the Augustiner beer garden or at Oktoberfest (where, incidentally, Lynen also corrected a doctoral thesis or two). Just like in the lab, it definitely did not go down well if you tried to steal away early on such occasions: “You sit right back down there. Don’t be so boring!” he would say in his thick Bavarian accent.

Feodor Lynen never had any intention of founding a school, yet that is exactly what he did. In the 37 years he taught, 88 undergraduates and doctoral students worked in his labs, and there were post docs and guest scientists as well. Many of his students were later appointed professors at universities or Max Planck Institutes. The “Lynen school” soon had offshoots all around the world.

Experiments lay at the heart of Lynen’s work. He did not think much of extensive literature studies, pure theory or wild speculation. “Nature is always unpredictable, and the only way to tackle a biochemical problem is to do experiments,” was his belief. But even he did not always find the answer in a test tube – sometimes it came to him on the way to the garden.
The Responsibility of Science

Tower ing bookshelves in the Gothic hall of Göttingen’s Paulinerkirche, which houses valuable volumes for the university library, and cranes in the old factory building of a closed-down Düsseldorf steel works provided inspiring backdrops for the prelude to the series of discussions entitled “The Responsibility of Science.” This marks the end for the Max Planck Forum of the anniversary year 2011 in Berlin and Munich. The series completes the retrospective of the history of the Kaiser Wilhelm Society (KWS) by examining what basic research means for today’s society.

The events were as diverse as the locations. The opening forum in Göttingen in late March discussed how research can function as part of and under the conditions of democracy. Guests included former MPS President Reimar Lüst, historian Manfred Heinemann (University of Hanover) and Jürgen Renn (MPI for the History of Science), together with the new President of the University of Göttingen, Ulrike Beisiegel.

The Düsseldorf-based Forum in mid-April was, in many respects, a response from the practical side of things and, with Ferdi Schüth and Dierk Raabe from the MPIs for Coal Research and for Iron Research, as well as Peter Dahlmann, Chairman of the Executive Board of the Düsseldorf Steel Institute, was attended by prominent guests with a wealth of knowledge from the worlds of science and business.

The structures of the KWS and the MPS were the focus of the Forum in Göttingen. According to Jürgen Renn, “looking at history to learn lessons for the future” is a useful exercise. In this case, analyzing the principles of research at the KWS proved a useful springboard for assessing the current situation in science. The Harnack principle is still significant as it constitutes a unique characteristic of the MPS compared with other establishments, providing for maximum freedom of research.

Agreeing on the importance of science for society: Jürgen Renn, Manfred Heinemann, Reimar Lüst, Jan-Martin Wiarda, Ulrike Beisiegel and Klaus-Armin Nave (from left).

However, the societal and political framework in which this principle is unfolding have fundamentally changed. Especially since the reform movements in the wake of the “Movement of ’68,” democracy, as Reimar Lüst stressed, has “clearly moved closer.” The necessity to publish research results, and increasing internationalization – even across political borders – ensures greater control of science. Mr. Lüst did, however, voice some skepticism as regards political and public involvement in the choice of research subjects. And the demand for scientists to be liable for their work, according to Reimar Lüst, should be fundamentally refused because “basic research cannot foresee its consequences.”

Nevertheless, according to Ulrike Beisiegel, scientific knowledge is the basis for political and societal decisions. Researchers are thus an important part of the democratic system. Freedom of research in a democracy is sometimes threatened more by seemingly ordinary everyday problems because the increasing bureaucratization of science often places time limits on creativity.

The Forum in Düsseldorf also stressed that a long-term strategy is ultimately the most important guarantee of scientific freedom. The MPIs for Coal Research and for Iron Research are two institutes that represent a line of continuity to the KWS. Their recipe for success in bringing together industry and science in a spirit of cooperation has worked well so far. There was no sign here of the concern of the Göttingen-based Forum regarding public interference in the choice of subject. On the contrary, there is a productive cooperation of application-oriented and basic research at both institutes.

Ferdi Schüth stressed that finding subjects often goes hand in hand with industrial interests – whenever there is also an “exciting research task” for scientists. In developing new methods of catalysis for biomass, for example, there is a win-win situation for all concerned. A similar argument was put forward by Dierk Raabe, whose Institute for Iron Research is opposed to application per se due to its research remit, because the institute “always bears in mind the industrial product.” Turbine blades or aircraft parts can also be further perfected by using knowledge from highly theoretical physics in material development, such as quantum mechanics.

Striving for knowledge and making a profit are not a contradiction against this backdrop. In fact, according to the key closing speech by Dierk Raabe, sweeping value judgments should be avoided. Science, which implicitly provides an added value, ultimately also contributes to the general prosperity of society and shows responsible handling of tax money.

At the end of this Forum, however, there was a sense that the “Max Planck model” gives scientists a remarkably high measure of freedom in the choice of cooperation partners: where industry calls for consistently calculable development plans, cooperation arrangements generally fail. Science needs a long-term strategy.
Solidarity with Japan

German scientists offer help after the natural disaster/New Max Planck Center

Many scientists, like anyone else who is part of an international network, sympathized deeply with their Japanese colleagues in March – and not only those in the areas affected by the earthquake and tsunami. Phil Selenko, a scientist at the Leibniz Institute for Molecular Pharmacology in Berlin had an idea, acted quickly, and the Nippon-ScienceSupport Internet platform was soon up and running. Max Planck institutes also promised their support – and the offer still stands.

Walter Stühmer at the MPI for Experimental Medicine in Göttingen, for example, considered it his duty to help. He works extensively with Japanese scientists and his wife was a Feodor Lynen research fellow in Japan. Both of them spontaneously decided to make their apartment available. “Our Japanese colleagues are welcome to live here and continue their research,” says Stühmer. The network also offers residencies and lab facilities “for scientists whose work is threatened by the consequences of the natural disaster.” Scientists want to use the links between the two countries to raise awareness of exchange programs, jobs and financial assistance so that their Japanese colleagues can continue to work on their projects abroad if necessary. This is a wonderful example of German-Japanese friendship, which celebrates its 150th anniversary in 2011: the first Treaty of Amity and Commerce was signed in 1861.

As a result, there is great solidarity at Max Planck institutes, where roughly 170 Japanese visiting scientists are currently working. For many years, the MPS has also enjoyed a close relationship with the Asian country, in particular with RIKEN, the association of top-level Japanese research institutes, as well as with the University of Tokyo. A total of 100 projects are currently being conducted with Japanese research partners and, last year alone, 26 MPI employees availed of extended research residencies in Japan. “The Max Planck Society and I personally would like to express our concern and sympathy to the people of Japan, those affected by this terrible tragedy and their families. The extent of the suffering and destruction is beyond our imagination,” wrote Max Planck President Peter Gruss to the presidents of Japanese research facilities.

Hideto Sotobayashi knows how precarious the situation is for people in Japan, particularly in the area around Fukushima. The chemist, who was a researcher at the Fritz Haber Institute in Berlin for decades, was a 16-year-old schoolboy in Hiroshima when the atom bomb was dropped. He is afraid that the victims of this disaster will suffer the same fate as he and many others did at the time of Hiroshima: “Many people believe that individuals who have been exposed to radiation are infectious. They are socially isolated.”

To ensure that this does not happen, scientific cooperation is being intensified. At the end of April, the MPS, in conjunction with RIKEN, established a Joint Research Center for Systems Chemical Biology. This provides a platform on which knowledge, infrastructure, new methods and technologies can be pooled. “When we rebuild our country, we must ensure that nothing stands in the way of the progress of science and technology,” says RIKEN’s President, Ryoji Noyori.

For many years now, Baufritz builders have taken nature as their model for healthy living with wood. Because nature shows best how hi-tech houses ideally work. By following this principle, Baufritz have developed patents for ingenious woodchip-based bio-insulation, enhanced wind proofing, protective coatings made from natural substances, earthquake proofing and our virtually maintenance-free Natural Silver facade.

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Includes a gym, swimming pool and tennis court, was designed to “cultivate international scientific relationships” and inspire the establishment of creative networks and exchanges of ideas with colleagues. Harnack House was returned to the Society in 1994 and a decision was made to remodel the building as a meeting place as quickly as possible. First, however, it was necessary to gain experience and to test out the operational concept, with the result that only parts of the building were renovated. Today, the building is a testament to a broken tradition rather than a bridge to a past with which today’s scientists can identify. Only fragments of the original features remain: the oak ceiling in the Bismarck Hall, the charming gold light fittings in the Mozart room and the red terracotta columns in the Liebig-Gewölbe dining hall. A 1950s style pre-
dominates throughout the house. Take, for example, the ballroom with its large-patterned flower-covered carpet. Or the old lecture hall where Max Planck and others revealed the secrets of science to the Berlin public in the 1930s. The lectern, seats and board have disappeared, and colorful fish now adorn the wall – relics from the disco era. Today, the room is a store-room, but must at least be maintained for the time being, adding to the operating costs.

But that’s all about to change, as the building’s value as a meeting place has increased – and continues to do so. Twenty years after German reunification, Berlin is now the focus of public interest. The new capital is attracting politicians, tourists and scientists, and the Max Planck Society is turning its attention to the jewel in the “German Oxford.” As a science district, Dahlem is more popular than ever – due mainly to the great success enjoyed by the Free University – as the opening of a conference hotel in Dahlem shows. Designed by award-winning architect Helmut Jahn, the building is also technologically state of the art and shows that science facilities must increasingly be designed with a focus on service.

The Max Planck Society is convinced that Harnack House, with its rich history, is competitive, and in March launched an architectural competition. The winning team’s designs give cause for optimism: the Lübeck-based partnership of Krause, Feyeraend, Sippel masterfully grafts modernity and comfort onto the historic structure, lending the building a clearly defined profile inside and outside. The plans include a new interior architecture, renovation of the lecture hall, ballroom and guesthouse, and the creative consolidation of the building as an ensemble. The team will be taking the existing structure into full consideration. Strictly speaking, the building consists of two separate parts, designed by Carl Sattler in 1929 to satisfy building regulations. These stipulated that only 30 percent of the site could be built on and that any building could have no more than two stories, so as not to adversely affect the rural character of the residential district. Sattler designed the main building and the lecture hall as two separate structures linked by an inconspicuous, low-lying connecting corridor. This was expanded in 1953 with the addition of the ballroom, destroying Sattler’s ensemble.

According to the architects’ plan, this could be restored if the new sections of the building were to be covered in wooden cladding. They suggest adopting the same approach for the 1960s guesthouse on the other side of the street, the interior of which will also be fully renovated. Both architects are working as a team with an interior designer and, to date, have designed hotels, some of which are located in historic buildings. They use a blend of purist, Japanese-inspired design elements in natural materials. Wood and textiles, offset by vivid colors, also dominate the design for Harnack House. Modern furniture with simple lines completes the look. It goes without saying that the lecture halls and guest rooms are equipped with state-of-the-art Internet access and conference technology. Nevertheless, the past has not been forgotten: the building’s signage not only helps to guide guests, it also provides information on the house and its history.

The space management concept remains unchanged: the Bismarck Hall will still be a lobby and the winter garden will still be used as a reception area. The functions of the rooms should be easier to recognize than they are today, a concept that is consistent with what Carl Sattler had in mind in 1929. He created an atmosphere that satisfied all the practical needs of scientific communication – from a casual chat in a lounge chair to a meticulously structured lecture. The building’s success proved him right. As Harnack himself envisaged, the building soon acquired an international reputation – one that is certain to continue.

Architect Carl Sattler deliberately planned Harnack House as a “timeless” building. Today, the ensemble looks like one long wing.
Typically German

A change of perspective – International officers consider local idiosyncrasies at their annual meeting

The 57 international officers of the Max Planck institutes gathering in May for their annual meeting experienced a change of perspective. In contrast to the format of previous years, where they took part in intercultural training sessions to learn more about how people in other countries behave, the spotlight this time was on their own German identity. Special presentations dealing primarily with changes in the rules for dealing with foreign guests rounded off the program in Stuttgart.

Every year, the international officers welcome large numbers of researchers from all over the world. They are the contact and first port of call for visiting scientists and their families and are faced with behavior, manners and communication styles that can differ significantly from those of their own culture. This makes country-specific, intercultural training a major part of the annual advanced training meeting to promote communication, tolerance, openness and flexibility toward guests.

The MPI for Solid State Research in Stuttgart was the host for this, the eighth meeting. Michael Eppard of institute management, and Birgit King, the on-site organizer, gave a warm welcome to the participants, who enjoyed three days of Swabian hospitality. First, they practiced self-reflection. After the focus in previous years on intercultural training for Eastern Asia, India, Russia and Eastern Europe, and the Middle East (Muslim countries and Israel), the subject this time was “cultural awareness – we Germans in interaction with other cultures.”

Four trainers from the company ICU-net outlined the various stereotypes of Germans abroad for those in attendance. They then went on to look – albeit with a humorous slant – at their own cultural idiosyncrasies and the awareness of the effect on others, in particular foreign guests, in order to be able to anticipate and avoid culture-induced conflicts. The typically German segregation of work and private life – based loosely on the saying “don’t mix business with pleasure” – was examined, as well as the very German virtues of objectivity and efficiency. Moreover, time, structure and planning in relation to living and working in Germany were touched on. In role-play situations, the international officers practiced communication strategies with the goal of breaking through hackneyed thought patterns.

At the traditional plenary meeting with specialist presentations, Birgit Haberberger from Administrative Headquarters, and Michael Felgenhauer, head of the award-winning Foreign Registration Office in Aalen, gave a very informative talk on the basic principles of the right to residence and foreign registration, with useful information on daily life in Germany from A to Z, covering subjects as varied as waste disposal and newspapers, an overview of do’s and don’ts in (professional) life, and insight into the culture shock phenomenon. The guide also contains information on the necessary formalities. The brochure has been delivered to the institutes and can also be downloaded as a pdf from the English and German MPS websites under “Careers – Working for the MPS.”

AN INTRODUCTORY GUIDE

A brochure entitled Living and working in Germany – A guide for international scientists at Max Planck Institutes has just been published. It offers foreign guests help in finding their bearings, with useful information on daily life in Germany from A to Z, covering subjects as varied as waste disposal and newspapers, an overview of do’s and don’ts in (professional) life, and insight into the culture shock phenomenon. The guide also contains information on the necessary formalities. The brochure has been delivered to the institutes and can also be downloaded as a pdf from the English and German MPS websites under “Careers – Working for the MPS.”

The International Officers at the Max Planck Institutes are the first point of contact for visiting scientists from abroad.
Max Planck Innovation is responsible for the technology transfer of the Max Planck Society and, as such, the link between industry and basic research. With our interdisciplinary team we advise and support scientists in evaluating their inventions, filing patents and founding companies. We offer industry a unique access to the innovations of the Max Planck Institutes. Thus we perform an important task: the transfer of basic research results into products, which contribute to the economic and social progress.