Vortrag Türkei, 01.-03.11.2018

From invention to innovation

A couple of years ago, the former president of the Max-Planck-Society in Germany presented an analysis of patents in the US American pharmaceutical industry. The most remarkable result was, that more than 70% of all publications which were the basis of the pharmaceutical inventions/innovations were produced in academic laboratories, were produced by what we call basic research. In our general understanding basic research is this type of research which is curiosity driven, not primarily application oriented, but directed towards a better and deeper understanding of the mechanisms underlying basic functions.

Being myself a medic, I should add, that to my understanding this definition is also correct in the research we are doing in medicine. However, most of us hope that our research somehow will contribute to a better understanding of certain diseases. But in most cases, our research is not product oriented, it is rather oriented towards understanding mechanisms of physiology, especially pathophysiology and identifying possible targets. And with this broad definition of course, most of the research, also in other fields, is somehow related to improve the

‘conditio humana’. This means that basic research is primarily a mechanism, which is process and method oriented, rather than product oriented.

And nevertheless, the transition from basic research into what we call applied research can be very short. Applied research has clear goals, in most cases we aim to come up with new and better solutions, with better products. And the more we learn, we can bridge the gap between basic and applied research in many cases better and better. What we also learned is that in many cases, problems and questions arise from applied research which deserve a new approach in basic research. Therefore, in our today’s life, we no longer describe basic and applied research as sequential events, but rather as an interactive, interwoven process where basic research can rapidly turn into applied research and vice versa. This is also the reason why in many companies, especially in the pharmaceutical industry, the paradigm of the last century, where basic research is being performed in academic laboratories and applied research in industrial laboratories is no longer valid. Nowadays, a lot of academic researchers in the medical field are translating their results from basic research into applied research, which is product oriented, while many industries, many companies spend a lot of money already in basic research, in order to be able to come to innovative products and solutions, early on. Related to this new paradigm is of course the question, who owns the patents, which is of paramount importance. In the

pharmaceutical industry the stagging of patent costs can be rather extensive if you have to take licenses for the target and/or for some specific methods. Also, therefore it can be quite interesting for companies to produce patents at the level of genes, proteins and others, areas which are the domain of what we used to call basic research.

Hence, more and more Public Private Partnerships exist between academia and the industry. But it also explains why the industry wants to have access to the patents early and academicians want to see their research results being translated rapidly to new products and eventually also in money. This desire can be fulfilled by active Public Private Partnership – or as an alternative by creating start-up companies out of academia. An endeavor which not only needs good science but especially excellent entrepreneurship. In fact, in recent years we have seen both: a phantastic increase in PPP-contracts worldwide and in Germany, but at the same time an enormous amount of start-up activities. Most of them in medicine and IT. Of course because of the high risks associated with drug Research & Development, many of the start-ups were not successful or only successful to a certain extent – but some of them made it and became very successful companies. This development is the reason why “big Pharma” has professionalized their search activities for new ideas, inventions.

One of the first start-ups in Biotech was Cetus, founded in 1971, followed by Genentech (1976), Biogen (1978), Amgen (1980) and many others followed. We know from history that in the field of IT in general and many other fields the same picture can be drawn.

Being a medic, I would rather like to concentrate on the pharmaceutical industry, which I know best and which I feel is still a perfect example to trace back the emergence of what we now call biotech industry and even better what is the basis for what we call molecular medicine or personalized medicine, today.

In the following I will try to show how this development started and how it transformed not only our understanding of basic mechanisms in biology but at the same time paved a fantastic avenue into new diagnostic and treatment options. It was Eugene Russell, who published in Science in January 2003 a paper, where he described how biotechnology became reality and started to transform medical research. And I will try to highlight important events which can give us hints how important inventions eventually were transformed into innovations.

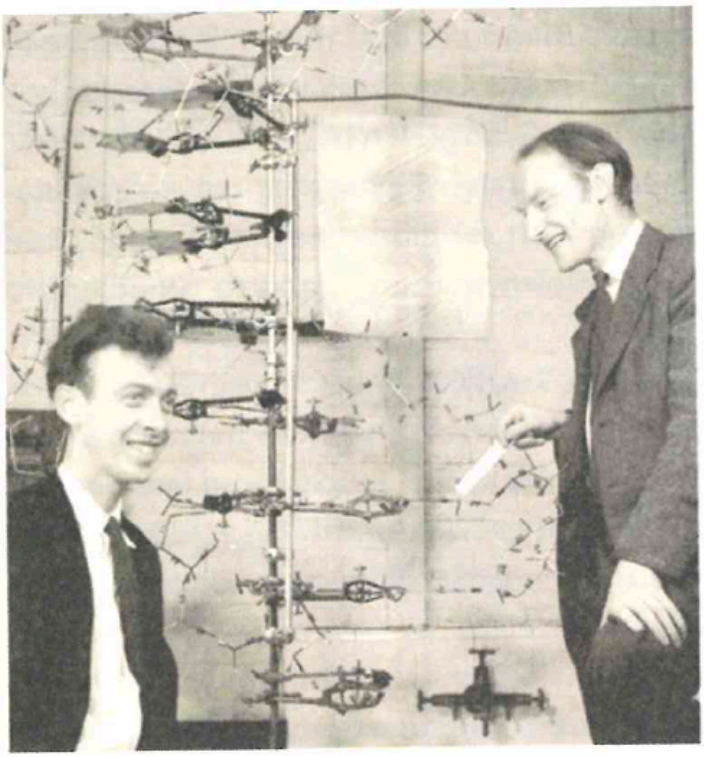
Eugene Russell writes that modern biotechnology started during a scientific congress in Honolulu in the year 1972. According to his narrative, Stanley Cohen, medical researcher, working at Stanford and the biochemist Herbert Boyer from

the University of California in San Francisco met and discussed Cohen's experiments, in which he managed to introduce plasmid DNA in Escherichia E. Coli. Boyer, on the other hand, had shown, that double stranded helix of the DNA could be separated into two single strands with an identical terminal region. Over dinner at Waikiki Beach – accidentally this shows that scientists never stop working – even when they enjoy good life in Hawaii. During this dinner they decided to combine these results in a series of experiments and in fact, they managed to clone DNA and to produce recombinant DNA. Eugene Russell considered this as the beginning of modern biotechnology.

No doubt, this is correct. However, it does not fully honor the research which has led to this revolutionary result. And this is why I am going to show why - what Russell describes as an initial step or the birth of biotechnology – I would rather like to call an intermediate step.

I will start the history with a german physiologist and anatomist, Johannes Müller, who in the 19th century realized, and then postulated, that all biological activities of human beings follow the same principals in physics, in chemistry and that this is true in all animals at the same time. And one should not discuss the development without Gregor Mendel, a monk, living in today's Slovakia, who described the basic laws or better: the principles of heredity, for the first time. A

big step forward brings me to Thomas Hunt Morgan, a man who is rightly called the father of genomic research. He could show that Mendel's laws, originally described for plants, is also true for fruitflies. And thereby proving, what Mendel postulated for plants., is true for animals as well. He gave evidence that genes are situated on chromosomes and that there is a clear order for the genes on the chromosomes. And finally, it was the description of the double helix by Watson and Crick who revealed the structure of the DNA who also gave descriptions on the role of RNA.

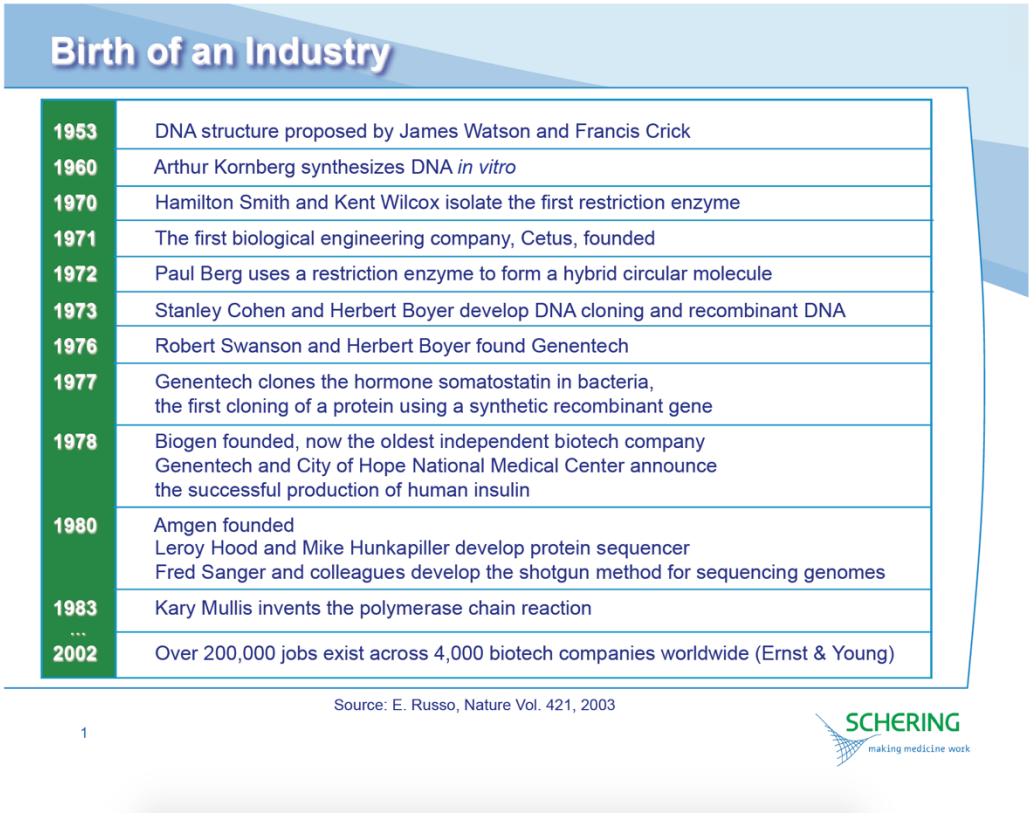


Fotografie von Anthony Barrington Brown: Watson und Crick mit ihrem Modell der DNA im Cavendish Labor in Cambridge, 21. Mai 1953

Abbildung 1
2003: Vor 50 Jahren entschlüsselten Watson & Crick die Struktur der DNA
(Quelle: Nature Vol. 421, 2003)

1. ***Slide***

The second slide is an adoption from Eugene Russell in his nature paper which shows the development of biotech, starting with Watson and Crick. In this slide, it becomes apparent, what I mentioned in my introduction. Scientists took an idea from basic research and created a company.



2. Slide

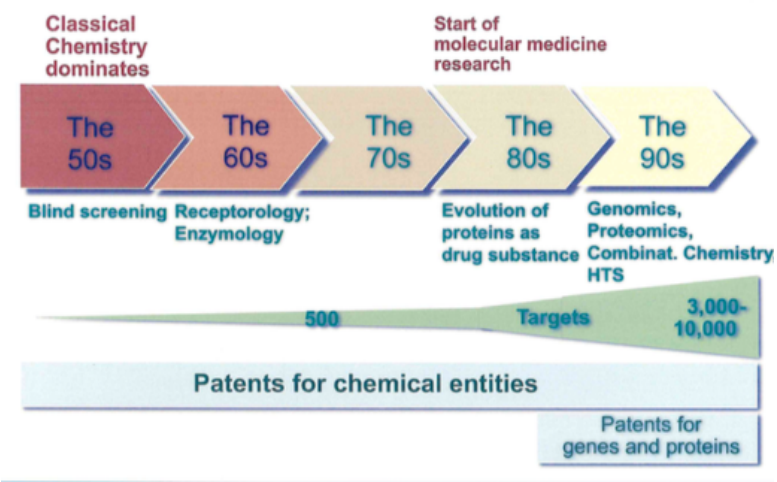
The foundation of these new innovative companies created quite some interest in circles of people who had money and were prepared to risk this money by investing it in these start-ups. The idea of venture capital was applied in the area of biotechnology. In fact, enormous amounts of venture capital was given to many biotech companies. Actually, however only later, also public money in

large quantities was given into this new field of research. Hence, it is fair to say that venture capital had a major impact on the development of modern biotechnology. Of course, this was a development which occurred in the USA first and for a pretty long time in the US only. But other countries followed to a certain degree. In Germany public money became available for this new research field, but we are still not good enough in providing venture capital to new technological areas, which is probably due to the rather high risk aversion in my country. I wish, that in your country the situation is better than in mine.

It was not too long, until human insuline could be produced in the year 1978. A breakthrough and proof of concept. Let me pause for a second and make the point, that this historic sketch, which is by far not complete and by far does not give justice to many, many researchers who contributed as well, show, that basic research in very different disciplines and labs led into what later became known as gene research, biotechnological research and today medical biotechnological industry. I don't know, when for the first time, people started to think, that this development could revolutionize our medical knowledge and our pharmaceutical industry. In fact, all of the health business, agro- and animal health business as well. Not to speak of the white biotechnology, the field of producing new basic chemicals, primarily used in industry.

But it is probably fair saying, that a few pioneers in the 70's and venture capitalists probably at this time, had a hunch that something really, really great and big would emerge.

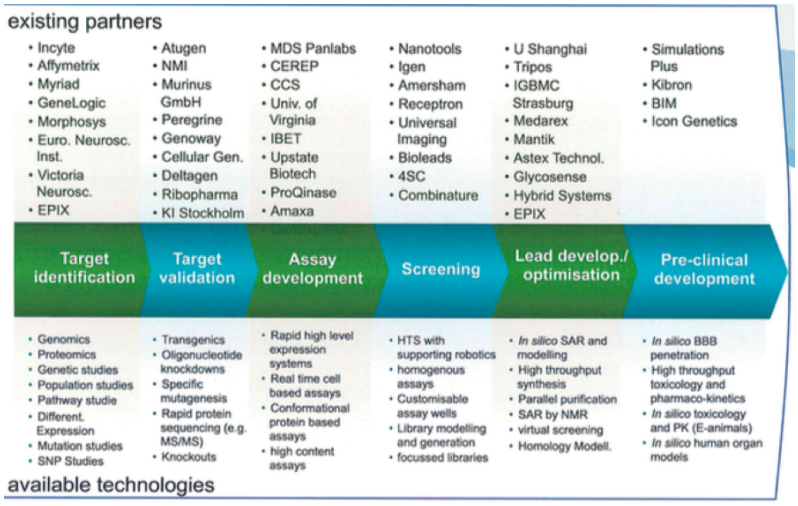
Let us now turn to the pharmaceutical industry: how was its development over the years, and when did people start to realize, that something was happening which would change their way of doing research.



3. Slide

It was probably in the 80's, when researchers in the pharmaceutical industry realized, that a new dimension of research was at the horizon. It was in those years when I left academia, the University of Heidelberg, and joined Schering in 1983. We decided in '84 that it could be an advantage to look into the developments of these new fields. We created an institute for gene biology with the university in Berlin as Public Private Partnership. From this time onward we sponsored the university in Berlin to support biotechnology in academia to quite an extend.

But we rapidly learned that the speed with which we tried to conquer this new field was not high enough and we created our in-house institute for protein- and genetic-research, followed immediately by the acquisition of a start-up company in the bay area in California, named Codon, soon followed by the acquisition of several additional biotech companies in this area.



4. Slide

At the same time, we were building a large network with companies and academic groups which helped us to professionalize and modernize our drug finding activities from target identification to pre-clinical development. And in fact, it only took until the year 1993, when we could bring our first biotech-product to the US market: a modified Interferon beta, then the first and only relevant drug for the treatment of multiple sclerosis. This now opened the field for Research and drug finding in autoimmune diseases. New approaches were found – today

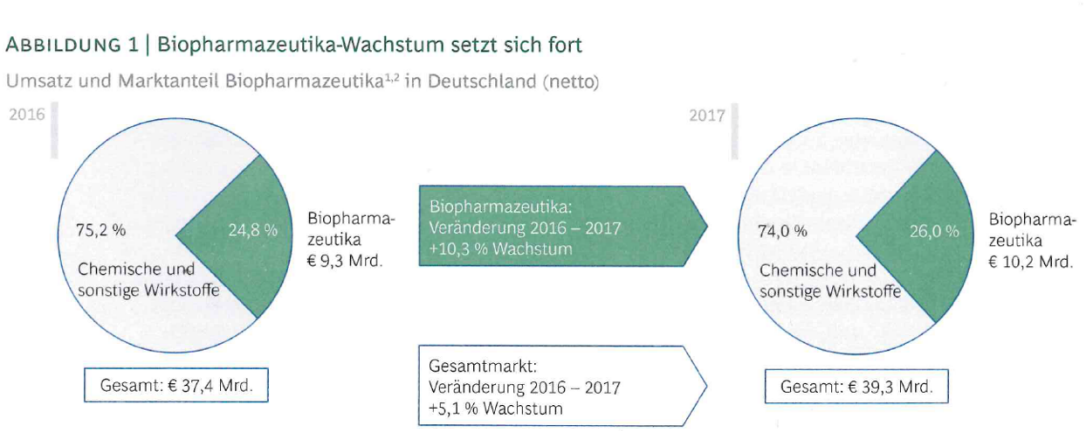
even small molecules. Application devices were developed. From then on, Research activities and publications in this field of biomedicine increased markedly and sustainably.

I think, that many other companies acted in a similar way especially in the United States, probably a little bit earlier, but in the end it was the same pattern: Acquisition of biotechnology start-ups, preferably those of course, who had products in development, derived from biotechnology, and we as a middle sized pharmaceutical company were probably forced more than others to enter into many, many Public Private Partnerships, in Public Public Partnerships, in order to be able to access all the modern technologies, which were needed to successfully develop innovative new drugs. The consequences for our research were clear: In the beginning, classical methods of drug finding were slowly but subsequently more and more rapidly replaced by in-vitro technologies: in pharmacology, biochemistry and in metabolic and toxicological studies. The era of molecular medicine had transformed our mode of thinking within only a few years. Our way of thinking, our way of doing experiments and our way of finding new drugs. All of a sudden trial and error to a large extend were replaced by hypothesis-driven, in the best sense, scientific approaches. High throughput in vitro approaches.

These days were interesting. Not only did we acquire start-up companies, but at the same time we also created start-up companies in which scientists who

wanted to be independent continued their research work in their own companies. The fact that all of a sudden so many new targets were available for drug finding, it was impossible for the companies, especially also for our company, to address all of those targets. We had to concentrate, we had to focus. And thereby some of the targets were given to individual researchers, who then founded their own company based on drug finding with those targets which we could not pursue. A phantastic era for innovations: both in big pharma as well as in start-ups.

So in these days, industry bought start-up companies, but also created new ones. What is the situation today? And here again I know, how it is in my country, in Germany.



[1]Netto-Gesamtumsatz (Apotheken- und Krankenhausmarkt im GKV- und PKV-Segment) nach Abgabepreis pharmazeutischer Unternehmen abzüglich der gesetzlich festgelegten Herstellerabschläge [2]IQVIA
Anmerkung: Biopharmazeutika = Arzneimittel, deren Wirkstoffe mit Hilfe gentechnisch veränderter Organismen hergestellt werden
Quelle: IQVIA Commercial GmbH & Co. OHG; BCG-Analyse

5. Slide

Today, 26% of drugs in the German market are based on biopharmaceuticals. This is one fourth of the whole market. Oncology and immunology are the fields which have the highest contribution to this turn-over. If we look at the pipeline, it is foreseeable that in the near future many more modern drugs will come out of the biotech efforts from big and small pharma companies.

Let me conclude: At least in the field of biomedicine it is a long way from the first invention to break-through innovations. In the beginning, it is not always clear, where the basic research will lead us. But ingenious research, ingenious combination of knowledge which is there: it can lead to breakthroughs.

Hence, it is obvious that basic research, curiosity driven research, is the humus of all. Here breakthroughs are made possible, here quantum leaps in knowledge, understanding and application of available knowledge is possible and reality. You cannot exactly plan and design inventions – you need best efforts, good hypothesis – but you already have to be aware that the outcome of your experiment can be different from what you expected – and you have to be prepared to interpret the unexpected properly. And, as stated before, you need endurance. This year's nobel prizes in medicine are perfect examples. The first: The question why our almost perfect immune system does not recognize tumor cells – a long, strenuous way in basic research to understand the phenomenon: and now we

have new treatment options. Second example: To apply evolution principles to optimize proteins – long time a field in which almost nobody believed in.

So, relevant questions about natural phenomena, carefully designed experiments - not to find products but rather to find an explanation for interesting phenomena, endurance and openness for the unexpected, all these are indispensable elements in basic research.

So my first message is: Research policies should be aware of this importance and should not ask too quickly for applied research, often neglecting basic research. A trend which can be observed in quite a few countries. Without a broad basis in basic research the ensuing applied research would soon die as well.

Second message: If we look at biotechnology, the success would not have been feasible without new materials, without new technologies, without new instruments, in brief without interdisciplinarity.

Message three: Public Private Partnership, cooperation across not only different fields, but also across different institutions, and across different financial sources, private and public money allows quantum leaps in the development of innovative products.

Message four: Most important is: Personalities who are convinced about their work, people with courage and vision.

Message five: Research institutions have to be autonomous in their decisions how to achieve their research goals and they in turn must give this freedom to their individual researchers, who then will based on their enduring curiosity find evidence and create inventions that work to proof the concept and finally enable the translation of their findings in developing new processes, methods, products.

Hence, we need individuals who have an imagination to what end, to what kind of innovation the basic results can eventually lead. These individuals must have this entrepreneurial spirit and they should look for partners who are exactly able to foresee the putative application of the invention. They need to network with synergistic partners, and in addition they have to find money for the applied research needed to develop the idea into a product.

In fact we all need the appropriate surroundings:

- Autonomy
- Infrastructure
- Money. Public money but also private money.

Public money is often granted on the basis of past performance, it is input oriented. Private money is often interested in future gains: it is output, outcome oriented. If both perspectives can be met by researchers: success is feasible. Finally, things work best, if relevant industries can be made interested in the early ideas. They provide output orientation but also professional advice on patents, concept proof, development skills and marketing information and skills as well as activities regarding market access and reimbursement issues.

So, new inventions nowadays – in addition to research in pharma companies - often also come from non-industrial sources but in many cases, they need industrial partners in order to succeed. Highly competitive academic research, integrated in and cooperating with other disciplines in international networks with a positive entrepreneurial surrounding in close connection with industrial enterprises – this might be the secret of a successful bridging for inventions into relevant innovations.

Let me come to an end. Innovations have different facets. Some of them are breakthrough innovations, they change the way of doing business radically as is the case for biotechnology in medical research where we learned to diagnose and to treat diseases on a molecular level and in some cases even at a truly

personalized level. Some breakthrough innovations created completely new business fields as is the case in the world of IT. But in addition there are also innovations that have a clear benefit, but not as dramatic as the first type which I described.

The pharmaceutical industry has many years been very successful and still is in slowly improving the efficacy of slightly modified drugs while at the same time reducing unwanted side effects. And to a large extent many of the innovations do have this character, which must not be underestimated. And furthermore there are also innovations in procedures - be it technical or be it process-oriented - which are for the medical field of great importance, but especially also in the manufacturing field where slight improvements in the process can yield an enormous outcome.

My last words are directed towards our modern societies and how they perceive innovations. There are societies where innovation is appreciated, is welcomed, mentally supported by the public. Therefore Research and the application of their results can flourish. Look at the United States and especially at Silicon Valley, today number one in IT. The same area some years ago was the number one area for biotechnology. Now both of them flourish – not only, but especially in California.

Societies, which are more critical and more hesitant towards innovations, towards the application of new technology are less successful. Therefore these societies have to learn and will learn to adapt. I am confident about this. To that end we have adopted fair processes to judge risk and benefit of new technologies. And we entertain an on-going process of risk-benefit-analysis over time rather than a one-time risk-benefit analysis only at the beginning of the process. A strategy which will help to secure longterm success. Sustainability!

A couple of years ago we in Germany were very critical towards new technologies, just to name the green biotechnology. And we still are. The consequence is clear: Today, we are no longer players in that field irrespective of the fact that many of the fears which existed when the technology came up, had not become reality. But now people are just averse against this new technology without underlying this with evidence and facts. And this clearly shows that the social climate, how we look at new technologies, does have a deep impact on our ability to be at the forefront of innovations or rather not.

Ladies and Gentlemen, since I am invited by an academy of science, I would like to finish my talk with a plea that academies do have a very special responsibility:

First to care for a scientific infrastructure which allows inventions and innovations.

Second academies have to care for the quality of the scientists and the scientific institutions of the society.

And number three: Due to the credibility of scientists, especially those in academies we have in our society, academies are well-suited places, to do something that we call public engagement. And this is to create opportunities, to create a place where scientists and the interested public come together and discuss scientific matters, which in most cases do have a social impact, where those issues are discussed at equal footing between scientists and the general public. Never in life before has the impact of science been so great for our daily life – and to recall what I said in the beginning on the 'conidtio humana', as impactful, as important as it is in our days. And innovations only improve our lives if they are meaningful for and expected and accepted by the people.