Tierversuche, Versuche mit und am Menschen: Grenzen und Möglichkeiten – Teil 2

Die Beiträge dieses Vorsymposiums werden in loser Folge in den *ALTEX*-Ausgaben 2, 3 und 4/2002 abgedruckt. Alle Beiträge zusammen erscheinen auch als *ALTEX*-Buch im Juli 2002

Animal Experimentation in Sciences: Sadistic Nonsense or Indispensable Necessity?

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Summary
The history of biomedical research clearly shows that, with exception of a very few, scientific findings could be realised only with the help of animal experiments. Unfortunately, in the past the life of animals was treated negligently and, at times, in fact criminally. Only the researchers' willingness to apply ethical principles toward laboratory animals could create a climate in which research is opening up to constructive, active animal protection and is ready to co-operate through the implementations of such programmes as the 3R-principle into daily practice. Using a number of examples, the article at hand tries to show that the dimensions concerning animal protection is very old indeed and that only a change of consciousness by the public and in research has created a situation in which a gentler treatment of life and life conditions of laboratory animals could be realised. A further development of "constructive" animal protection within the industrialised nations is only possible with this back ground. Without such a development, biomedical research is bound for deficits in one way or another. It will be loosing itís medical and economical opportunities and with it, it's meaning for man.

Zusammenfassung: Tierversuche in der Wissenschaft: Sadistischer Unsinn oder Notwendigkeit?
Die Geschichte der biomedizinischen Forschung zeigt auf, dass nur wenige Erkenntnisse der modernen Medizin ohne die Hilfe von Tierversuchen gewonnen werden konnten. Leider ist in der Vergangenheit häufig nachlässig, ja manchmal sogar kriminell mit dem Leben von Versuchstieren umgegangen worden. Erst die Bereitschaft der Forscher, ethische Prinzipien auch auf Versuchstiere anzuwenden, hat ein Klima geschaffen, in dem die Forschung offen ist für den Wunsch nach konstruktivem Tierschutz und selber aktiv daran mitarbeitet, z.B. durch Umsetzung des 3R-Prinzips in die tägliche Praxis. Im vorliegenden Artikel wird an einigen Beispielen verdeutlicht, dass die Diskussion über den Tierschutz sehr alt ist, dass aber erst die veränderte Bewusstseinslage der Öffentlichkeit und der Forschung Raum für einen schonenden Umgang mit dem Leben und dem Befinden von Versuchstieren geschaffen hat. Nur auf diesem Hintergrund ist die Weiterentwicklung des konstruktiven Tierschutzes in den Industrienationen möglich. Ohne diese Weiterentwicklung wird aber die biomedizinische Forschung in der einen oder anderen Richtung defizitär und verliert daher ihre ökonomischen und medizinischen Möglichkeiten und damit ihre Bedeutung für den Menschen.

Keywords: history of medicine, 3R-principles, animal welfare, biomedical research

1 Introduction: About the temptation of experimentation

Since the beginning of human consciousness man has tried to understand his position in the world by means of observation, reflection, but also by experimenting with animals, with his fellow man and also with himself. For as long as this thirst for knowledge has existed there have been admonitory voices and legal guidelines constantly re-defining possibilities and setting limitations on research and recognition.

There are reports from the renaissance, stating that the illegal *post-mortem* examinations performed by some researchers including Leonardo da Vinci (comp. Fig. 1) on persons put to death by hanging were carried out on special tables where the tabletop could be flipped when required: On one side was the hanged person, on the other a pig, both strapped on and opened up. By flipping the table – so the tale – the police could be led to believe the organ-removal had been performed on the pig.

This old record also has a symbolic meaning: Man and animal are like the two sides of a coin. Both together consti-

Fig. 1: Leonardo da Vinci (1452-1519); anatomical drawing

tute the value, one side without the other is inconceivable. It was therefore the aim of this symposium to discuss both sides: Possibilities and limitations of the animal experiment in just the same way as examinations with and on humans.

Most researchers are aware of the fact that the right of free research and especially research involving humans and animals is a relative and limited right which needs justification by conscience, by society and also towards the sacrificed creature or the *instrumentalised* individual. Continuously renewed reflection on the possibilities and limitations in experimenting with animals and man is necessary and should remind us that even the most advanced molecular biology can only be of public benefit if it is gained with care, modesty and responsibility and within continuously renewed rules of (bio)ethics.

2 Animal in the service of the human race

Man's first companions were his domestic animals. They were protected by him, but served him in many ways by providing nourishment and clothing and by safeguarding him. All of these functions implied that the animals were killed at times, either to provide meat and leather or in defending man against enemies. During historical times, man tried to gain insight into the functions of the human body by experimenting with animals. It is said that Democritus (from Sicily) performed experiments on domestic animals. He was declared insane by the people of Abdera. However, the story is that Hippocrates (Fig. 2), being asked to judge, declared the people of Abdera insane but Democritus wise (because he wanted to increase his knowledge and skills as physician).

Most of the major breakthroughs in medicine resulted from experimentation on animals, although some animal protectionists deny this. For thousands of years no physician understood the function of the heart and its connection with large arteries and veins. Only after Harvey (1671, Fig. 3) dared to investigate the cardiac function in living animals, the mechanics of the blood circulation and the role of the heart as its pump were discovered. How could we ever understand our cardiovascular diseases without understanding the circulation? At the same time, A. von Haller (Fig. 4) discovered how nerves make muscles contract, and Galvani proved the electrical coupling of the neuro-muscular system.

All these eminent scientists discovered and tested their concepts in animals. Without them we could not have overcome classical Hippocratic medicine and would still enjoy the dubious benefits of bloodletting and forced purgation by laxatives. Instead, based on the work of these and many other researchers of the 17th and 18th century, our modern, scientific medicine developed, which today allows us to treat many patients – unfortunately not all – effectively on a rational basis. It comes as no surprise that almost all Nobel Prizes in medicine were awarded for results partly obtained from animal experimentation (Tab. 1).

How much has been achieved is illustrated by comparing the situation of

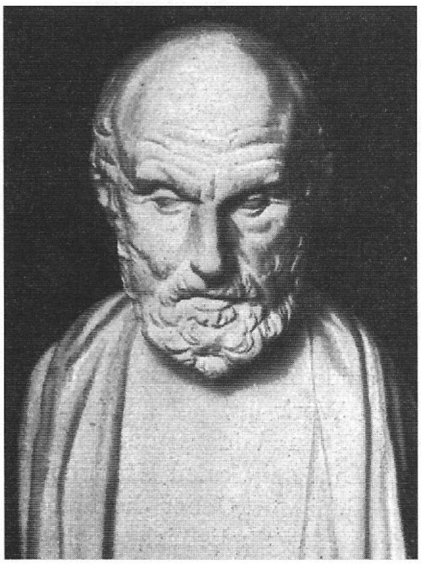

Fig. 2: Hippokrates (ca. 460-377 v. Chr.)

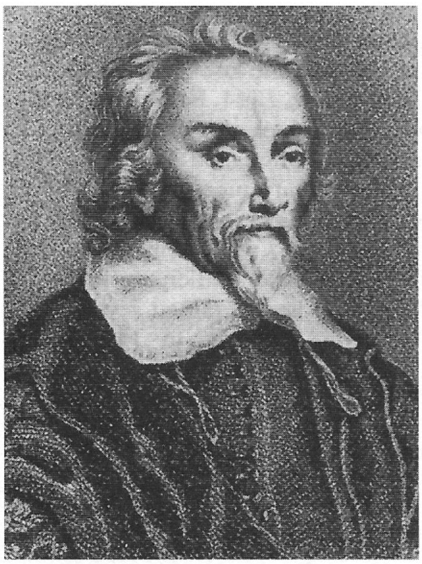

Fig. 3: William Harvey (1578-1657)

Fig. 4: Albrecht von Haller (1708-1777)

patients suffering from rheumatic heart diseases 100 years ago with today's situation: In his famous article about the "The Value of the Pathological Experiment", Rudolf Virchow (1881, Fig. 5) complained at the International Congress on Pathology, held in London in 1881: "Despite all the successes of modern medicine, including new insights and better treatment of many diseases, one argument may correctly be made by the animal protectionists, namely, that up until now it has been impossible to prevent or cure the rheumatic heart diseases. They still cause many young and old people to either suffer or die early" (translation by the author). Today, 100 years later, this disease is no longer a problem. Antibiotic therapy of tonsillitis and similar infections prevents the development of this disease. If it does occur, which is now very rare, the crippled heart valves can be repaired by a routine surgical procedure. Both forms of treatment, the antibiotic therapy as well as the surgical procedure, could not have been developed without animal experimentation. Moreover, only 50 years ago about 40% of the northern European population died of infectious diseases. Due also to antibiotics, the figure is less than 5% today. These two examples should suffice to show that all statements claiming that medical animal experimentation has not helped mankind are incorrect. Nevertheless, we have to admit that other diseases prevail as causes of death and that most of them, including many forms of cancer, cannot be cured at present despite the sacrifice of many thousands of rats, mice and other animals. The continuing use of animals for cancer research therefore needs particular justification, which is done regularly (Sedlacek, 1986).

Tab. 1: Nobel prizes based on animal experiments

Up until 1982, a total of 54 Nobel prizes were awarded by the scientific committee in Stockholm for the discovery of an effect or structure of therapeutically important drugs. Thus, the decisive stages in the development of new drugs gained world-wide recognition. Animal experiment and animal observation were the basis of these achievements which helped to increase our life expectancy considerably.

year	scientist	animal	contribution
1901	von Behring	guinea pig	development of an antiserum against diphtheria
1902	Ross	dove	investigation of the life cycle of parasites causing malaria
1904	Pawlow	dog	animal reactions to different stimuli
1905	Koch	cow sheep	research on the pathogenesis of tuberculosis
1906	Golgi	dog horse	characterisation of the central nervous system
1907	Laveran	bird	role of protozoa in pathogenesis
1908	Metschnikow Ehrlich	bird fish guinea pig	immune reactions and functions of phagocytes
1910	Kossel	bird	findings in cell chemistry through protein research using nucleic substances
1912	Carrel	dog	work on vascular suture and the transplantation of blood vessels
1913	Richet	dog rabbit	mechanisms of anaphylaxis
1919	Bordet	guinea pig horse	mechanisms of immunity
1920	Krogh	frog	discovery of the capillary motor regulating mechanism
1922	Hill	frog	oxygen and lactate metabolism in the muscle
1923	Banting, Macleod	dog rabbit	discovery of insulin and the mechanism of diabetes
1924	Einthoven	dog	discovery of the mechanism of the electrocardiogram
1928	Nicolle	monkey pig rat mouse	pathogenesis of typhus
1929	Eijkman Hopkins	chicken	discovery of antirheumatic and growth stimulating vitamins
1932	Sherrington Adrian	dog cat	functions of neurons
1934	Whipple Murphy Minot	dog	liver therapy in cases of anaemia
1935	Spemann	newt	discovery of the organizer effect in embryonic development
1936	Dale Loewi	cat frog bird reptile	chemical transmission of nerve impulses
1938	Heymans	dog	function of sinus and aorta in the regulation of respiration
1939	Domagk	mouse rabbit	antibacterial effects of prontosil
1943	Dam Doisy	rat dog chick mouse	discovery of the chemical nature of Vitamin K
1944	Erlanger Gasser	cat	discoveries relating to highly differentiated functions of single nerve fibres
1945	Fleming Chain Florey	mouse	cure of bacterial infections with penicillin
1947	Carl Cori Gerty Cori Houssay	frog toad dog	discovery of the course of catalytic conversion of glycogen
1949	Hess Moniz	cat	functional structure of the brain as co-ordinator of inner organs

Fig. 5: Rudolf Virchow (1821-1902)

3 Limits of animal experimentation: human health vs. animal protection

Many people accept that cause and treatment of serious diseases, such as cancer or cardiac infarction, should be investigated in animals, but they reject animal experimentation on new chemicals, household equipment, car-parts or cosmetics. At first glance, almost everyone would agree with this position. The problems arise when we look at it in more detail. Central Europe's population has increased approximately fivefold within the last 100 years. The average life expectancy has increased from 30-40 years to 70-80 years. This progress occurred despite increasing traffic, more air and water pollution, etc. It is based on a constant improvement of our technical and chemical knowledge, devices and tools. Consequently, for example, new chemicals with unknown risks but potentially superior qualities are produced every day. If we block innovation in this area, progress towards safer, faster, cheaper and more economical drugs, textiles or cars would be impossible, and the growth of our economy would come to an end – the results of this are felt in every economic recession. Alternatively, if we allowed all new chemicals to come in contact with our living environment without prior testing of their toxicity, we would increase the hazards to man. A decade ago, new chemicals for human use were not tested in animals. Today, we have realised that some stains, agrochemicals or wood protectants are toxic.

year	scientist	animal	contribution
1950	Kandall Hench Reichstein	cow	anti-arthritic effects of suprarenal hormones
1951	Theiler	monkey mouse	development of yellow fever vaccine
1952	Waksmann	guinea pig	discovery of streptomycin
1953	Krebs Lipmann	dove	characterisation of the citric acid cycle
1954	Enders Weller Robbins	monkey mouse	culture of polio virus leading to the development of a vaccine
1955	Theorell	horse	nature and mode of action of oxidation enzymes
1957	Bovet	dog rabbit	production of synthetic curare and its effects on vascular and smooth muscles
1960	Burnet Medawar	rabbit	understanding acquired immune tolerance
1961	von Bekesy	guinea pig	physical mechanism of stimulation within the cochlea
1963	Eccles Hodgkin Huxley	cat frog octopus crab	role of ions in the stimulation and inhibition of peripheral and central nerves
1964	Bloch Lynen	rat	regulation of the cholesterol and fatty acid metabolism
1966	Rous Huggins	rat rabbit chicken	tumour-causing viruses and hormonal cancer therapy
1967	Hartline Granit Wald	chicken rabbit fish crab	primary physiological and chemical visual processes in the eye
1968	Holley Khorana Nirenberg	rat	interpretation of the gene code and its function in protein synthesis
1970	Katz von Euler Axelrod	cat rat	mechanisms of storage and release of neurotransmitters
1971	Sutherland	mammal liver	mechanisms of hormonal action
1972	Edelman Porter	guinea pig rabbit	chemical structure of antibodies
1973	von Frisch Lorenz Tinbergen	bee bird	development of social behavioural patterns in animals
1974	de Duve Palade Claude	chicken guinea pig rat	structure and function of the cell
1975	Baltimore Dulbecco Temin	monkey horse chicken mouse	interaction between tumour viruses and genetic material
1976	Blumberg	chimpanzee	slow viruses and new mechanisms of the dissemination of diseases
1977	Guillemin Schally Yalow	sheep pig	hormones of the hypothalamus
1979	Cormack Hounsfield	pig	development of computer assisted tomography (Cat Scan)
1980	Benacerraf Dausset Snell	mouse guinea pig	identification of histocompatibility antigens and their mechanisms
1981	Sperry Hubel Wiesel	cat monkey	processing of visual information by the brain
1982	Bergström Samuelsson Vane	ram hare guinea pig	discovery of prostaglandins

This toxicity can now be foreseen by animal experimentation, but only to a limited degree by tissue culture experiments (Cramer, 1988; Zell, 1987).

Again, history teaches us what will happen if we do not test for toxicity. For example, about 100 years ago the radioactive elements radium, radon and thorium were discovered and used in medicine and industry without prior animal testing. A few years later many physicians, patients and industrial workers died from radiation-induced cancer, because they had been exposed to the new elements before their hazards had been investigated. In retrospect, it is obvious that animal experimentation of the type we use today would have saved the lives of many people, among them the physicist Röntgen, who discovered the X-rays (Fig. 6).

In my mind, both alternatives, an immediate and complete block of chemical-technical innovation as well as allowing direct exposure of man to new materials and chemicals is unacceptable for ethical reasons. Nevertheless, new methods for assessing the potential toxicity of new materials in the test tube should be developed quickly in order to reduce further testing in animals. Many discoveries have been made recently which allow, for example, prediction of the likelihood of a new compound inducing cancer in man from the effects on yeast cells or bacteria. This shows that science does strive towards animal-free testing (replacing their use), but for the foreseeable future only the reduction of the numbers of animals sacrificed and the refinement of animal experiments, i.e. minimising their suffering, are realistic goals, because effects on many physiological functions can only be tested in animals and not in bacteria and other simple organisms.

Is the same reasoning pertinent to the development of cosmetics? Apparently, no-one will die if no new cosmetics are introduced. On strict ethical grounds research on cosmetics or, as we may call it more fashionably, "life style" drugs must be banned. On the other hand, since Adam and Eve, women have tried to improve their appearance by using "cosmetics". New pigments, new creams, new skin hormones are continually being developed and produced. Without new pigments, the introduction of new fashions is difficult. When questioned, most women admit that they feel better when using fashionable cosmetics and, consequently, they are willing to "pay" for them. Should they also pay with their health when they use new but untested cosmetics? On the other hand, people who suffer from occasional headaches, which are not lethal either, also feel better when they use analgesics. Moreover, if they had no analgesics, some would be unable to maintain their social contacts and to carry on their normal work. Consequently, should experimentation to develop new analgesics also be banned !? Not quite, some forms of chronic pain have disease quality. They disable sufferers and may even lead to suicides. Experiments to cure this pain appear perfectly legitimate, and the use of new analgesics to treat casual headache is a welcome side product of the more ethical attempts to cure serious pain. How can we transfer these sophisticated arguments? If one does not use cosmetics and has no headaches, the price of developing new analgesics and cosmetics in terms of animal suffering due to testing their possible toxicity appears unacceptably high. To the consumer, however, the same price may appear acceptable. Amazingly, some of those who demonstrate against animal experimentation not only owe their life to recent bio-medical progress, but also continue to use headache pills and cosmetics.

Fig. 6: Wilhelm Konrad Roentgen (1845-1923)

Of course, one could argue that women and men, who want modern, fashionable cosmetics (textiles, fragrances) should test the toxicity on their own skin and not on rabbits or pigs. A brave suggestion, and some would be brave enough to do it. But what would happen if women who have used a new pigment in their 20's die from skin cancer in their 30's? Not only will they suffer, but also their children who lose their mothers, and their husbands who lose their wives. Of course, science, industry and governments would be accused of negligence! Even the suggestion to use natural products as cosmetics instead of chemicals is not really convincing in the long run. The recent trend towards plant extracts and other "natural ingredients" in cosmetics has increased the incidence of allergic skin reactions considerably. Moreover, the last years have demonstrated that many plants contain carcinogenic substances which, if administered or applied for prolonged periods of time, may cause more cancer than many well tested and well investigated pure chemicals.

In conclusion, as simple as decisions about the need for animal experimentation may appear at first glance, looking at the subject in more depth shows that it isn't that easy, and that many people who are vehemently against animal experimentation enjoy and demand, knowingly or unknowingly, the benefits of new drugs, cosmetics or textiles – all being developed employing safety experiments on animals. To solve this dilemma implementation of the 3R-principle is mandatory.

4 Modern laws for the protection of animals: more bureaucracy and less research?

Driven by the scientists' bad consciences, the pressure of animal protectionists, but also, admittedly, the fact that some scientists have abused animals unnecessarily, laws (TierschG., 1998) and ethical guide lines (Deutsch and Schreiber, 1985; Bochenski et al., 1986; SAMW/SNW, 1996; Riecker, 1984;

Lembeck, 1988) for the protection of animals have been installed in many countries. For some scientists they may go too far, for most animal protectionists they appear to fall short of the necessary. The latter claim that, in their mind, unnecessary animal experimentation, i.e. repetition of experiments, quality and safety control of new but useless drugs, etc. are still possible. They overlook that experiments are not always conclusive and testing a hypothesis twice is more than a repetition, it is often a necessary confirmation. Whether a drug is really useless becomes clear only in retrospect! For example, about the 20th sulfonamide introduced into the clinic (5 to 10 would have been enough, many would say) turned out not only to kill bacteria, as all others do, but to lower high blood sugar in diabetic people as well. Without the clinical use of this 20th compound, this new effect would not have been discovered. The class of orally active antidiabetic drugs would not have been developed and many patients would not enjoy this new, effective and comfortable therapy. As pointed out previously, the scientific and economic development of our countries depends on the development of science and technology, in part involving animal experimentation.

Certainly, much can still be improved in detail, but in general, animal protection is a prevailing aim and without animal experimentation, progress is seriously hampered. The behaviour of a new drug in the body, for example, can be tested only in the body and not in a test-tube or tissue culture dish. On the other hand, scientists are facing serious problems. For each type of experiment, they have to file a protocol and have it approved by an Ethics Committee consisting of researchers and representatives of animal protection groups. Rejections are frequent to occur and certain types of disease models in animals, e.g. the so-called adjuvans arthritis, a model of rheumatoid arthritis, are practically banned in Germany for example. This means more bureaucracy for the scientists in addition to the large burden they already have to navigate in our over-regulated and complex society.

Nevertheless, many questions may be answered by using tissue cultures and many animal experiments could be spared with the help of alternative methods, which were often developed before animal protectionists demanded them, because most scientists hate killing animals and *in vitro* tests are often less expensive. On the other hand, some animal protectionists have turned their activities into a business which supports their life and may even allow them early retirement from their learned profession (Nathusius, 1990). Some of them may even start "freeing" animals, only to let them die in the wilderness, or to harass scientists and their families. These activities are a serious threat to all attempts to reduce, refine and replace animal experimentation.

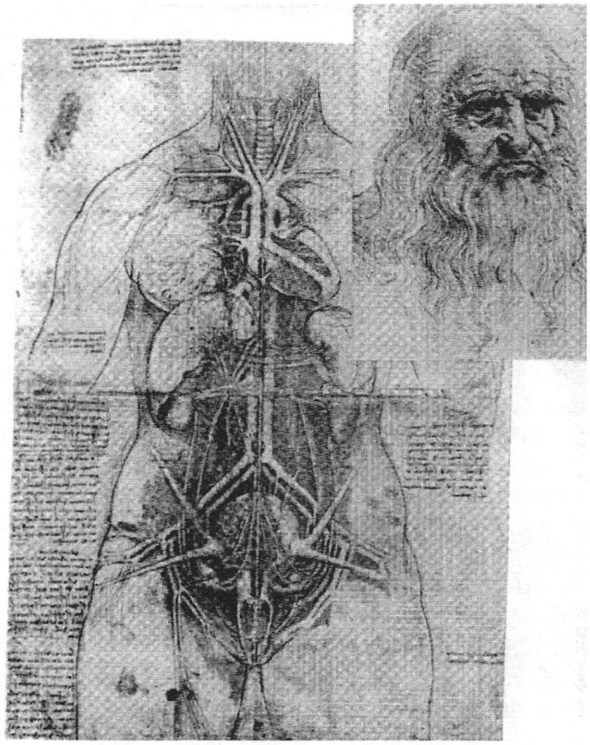

Fig. 7: Leonardo da Vinci (1452-1519); early anatomic figure

5 The need for equal standards

Modern science and technology has its cradle in Europe. Without animal experimentation scientific progress, research on and in humans – e.g. anatomical investigation as performed by Leonardo da Vinci (Fig. 7) – would have been impossible. Increasing the bureaucratic hurdles will interfere with the progress of research and development. The industry already feels the consequences. Many companies now perform research involving animals in Eastern European, South American or Asian countries – more to save time than money. A new generation of researchers who wish to learn from animal experimentation, like Harvey, will either go to these countries to achieve adequate education or neglect gaining expertise in areas of research which are of considerable importance for the scientific and technological development of our countries. The universities are no longer in a position to teach students how to dissect animals and how to perform simple physiological or pharmacological experiments, although these experiments are no more harmful than what a physician does to his/her patients. Moreover, painful animal experiments are performed under anaesthesia. Our students lack this education. They will later become physicians. Since they did not learn surgery with the help of animals they will have to learn to cut and sew the tissue on patients. Most Germans will not want to be the substrate of this learning process. If so, we will have to import qualified surgeons, have our physicians trained or get our surgery abroad. Either option is dissatisfying.

Moreover, research at European universities is becoming increasingly difficult and inefficient under such conditions. In the long run this will mean that young, qualified scientists will emigrate and thus endanger the European future of which, many hope, a new chapter is just beginning.

A solution to this dilemma may come from the increased awareness of all scientists of the ethical problems involved in animal experimentation. Only then the consequent implementation of the "3R-

Principle" will not only be furthered by private foundations or governmental regulations, but deliberately performed by all scientists. That means that similar standards have to be implemented world-wide. It is not acceptable that primate experiments are allowed without ethical control in some countries, that thousands of dogs are killed without anaesthesia in others and that rodents are not regarded as animals worthy of any protection in the United States, while Western Europe – for good reasons – requires air conditioned animal facilities and qualified personnel for all animal species. Only acceptance of similar ethical standards will guarantee animal protection world-wide.

6 We are all part of nature

Most scientists will welcome any support which allows the development and use of more refined methods in necessary animal experimentation, even if they are more expensive. They realise that the right to do research is a relative right which has to be justified to the individual consciousness as well as the ethical limitations outlined by our society. The sacrifice of animals can only be justified if all precautions are taken to do experiments as innocuously as possible and only if replacement is impossible.

Refinement in research is possible e.g. by using non-invasive imaging techniques. Fig. 8 shows a functional image of the brain of a rat (under anaesthesia) following a short pull on one whisker. The increased blood flow in different areas of the brain indicates a nociception (pain) related information processing and allows us to follow the effects of repetitive nociceptive stimuli (chronification) as well as of drugs that enhance or reduce chronic "pain".

Maybe the increasing awareness of animal suffering stems from a new scientific view on globalisation. Many of us believe that our whole world is a large single organism in which every human being as well as every animal or plant is a part, like a cell is in our body. This new understanding of the living earth has been named the "Gaia" concept. In this concept, killing animals means killing parts of ourselves. In face of the apparent mightiness of modern molecular biology, a new dimension of decency and humbleness is required. It will further animal protection much more than new laws or bureaucratic hurdles.

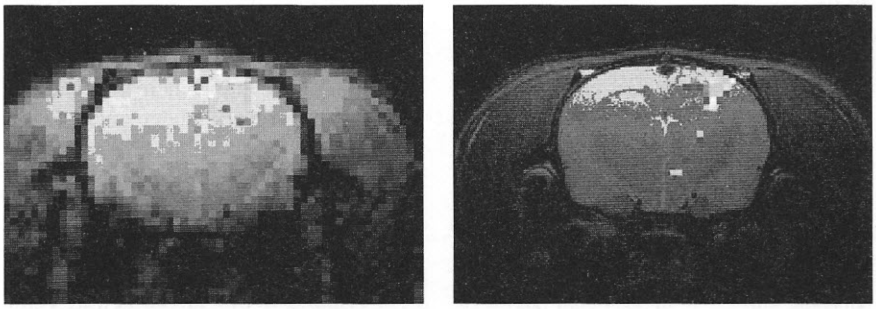

Fig. 8: Rat brain: fMRI in brain barrel cortex II, fMRI Sequenz GEFI-TOMO; FOV: 3.0 x 3.0 cm; Matrix 64 x 64 x 3; Res.: 469 x 469 x 500 µm, TR: 164.3 ms; TE: 15.2 ms; RF: 4; NEX: 1; MR-scanner: BRUKER BioSpec 47/40 (Courtesy: A. Hess, Department of Pharmacology and Toxicology, Erlangen)

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