The Magazine from Carl Zeiss

Innovation

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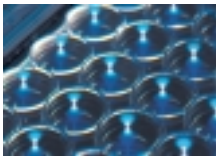


A Broad Spectrum

Molecular biology for medical progress

The terms "molecular" or "molecular biology" frequently appear in the names of institutes and even companies. The term "molecular" describes facts about molecules in general. As an interdisciplinary subject and subdiscipline of biology, molecular biology combines biological, physical, chemical, medical and pharmacological methods. Examinations in this discipline are focused on structure, regulation of growth and interactions of cells. Using elaborate molecular-biological screening techniques, pharmaceutical research endeavors to discover highly specialized medical drugs. Screening techniques are complex technologies which can accelerate and ultimately facilitate the search for new drugs. The new, up-and-coming discipline of molecular medicine makes more and more use of molecular-biological techniques for the analysis and treatment of diseases.

Laser scanning microscopy and laser microdissection number among the many options open to molecular research and analysis. Genetically caused diseases can be visualized using molecular-biological tools and microscopes.

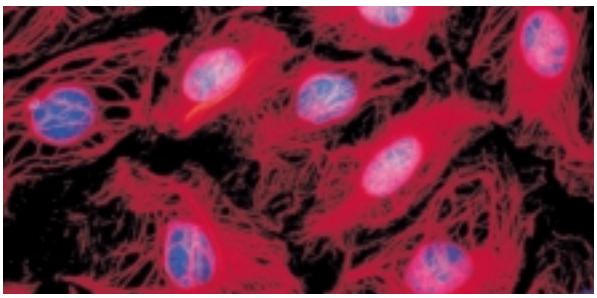


Fig. 1: Intermediary Keratin filaments (red), DNA (blue).

Diversity of life and the environment

Laser scanning microscopy brings new life to insects that are thousands of years old. Animals trapped in amber are visualized precisely and in great detail, thus deepening interested viewers' understanding of the subject. During an expedition cruise of the German research vessel METEOR off Namibia's coast, an international research team examined the diversity of animal life in the water. The environment does not necessarily profit from spectacular events; however, in 2002, the winner of the world's most challenging sailing competition, the Volvo Ocean Race, was not only the "illbruck", but also the environment. All the yachts participating in the regatta were equipped with measuring systems that recorded data during the entire race. This data is now being evaluated by the institutes involved. And during this year's environment summit in Johannesburg, the laser all-dome projection system fascinated the participants and led them into enthralling real and virtual worlds.

Fig. 2: "Nordhausen" balloon above the Saale river near Halle, Germany.

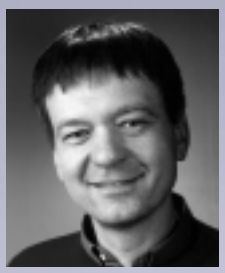
Innovation – the motor of success

In the jubilee year of the **Tessar®** camera lens, unique aerial photos taken during a balloon ride demonstrate the excellent features of the lens. *Ernst Wandersleb*, an enthusiastic balloon rider, took the opportunity of a trip to test and further develop the lens for aerial photography. In the Antarctic, cartography pioneers are honored: many geographic places are named after designers of optical measuring instruments. Outstanding feature films like "Lord of the Rings" truly come to life through nature pictures and large picture formats. Movies are produced in difficult conditions, and cine lenses have been developed for these conditions. In October 2002, a further award was presented to laser scanning technology: the centerpiece of the **LSM 510 META**, the multichannel detector, received the so-called "Oscar of Inventions", the R&D Award. The guiding principle behind all activities of Carl Zeiss always was to enable science and technology to go beyond what man can see. The company slogan "We make it visible" carries this tradition on into the future.

November 2002

Dr. Dieter Brocksch

High Throughput Screening



Christof Fattinger

The future of today's pharmaceutical research and drug discovery is based on millions of optical analyses of the molecular activity in biological microsamples.

Gaining know-how through automation

Enhancing knowledge through completely automated experiments in extremely small biological samples is one of the most exciting innovations of our times. The new findings are achieved by sophisticated, integrated hardware and software systems. These new tools permit biological, medical and pharmaceutical research to examine and characterize the biological activity of small, organic molecules in large chemical libraries comprising several million compounds. This and the pioneering progress in fluorescent sample technology offer the scientist the possibility of quantitatively and qualitatively examining the interaction of synthetic molecules with proteins identified as a target molecule for a potential drug – and all with pinpoint accuracy. The combination of molecular biology, medical chemistry and molecular analysis by automation with state-of-the-art process control and data capture essentially influence and change the way we work in all fields of the life sciences. More than anywhere else, this technology is proving to be a great success in pharmaceutical research and drug discovery.

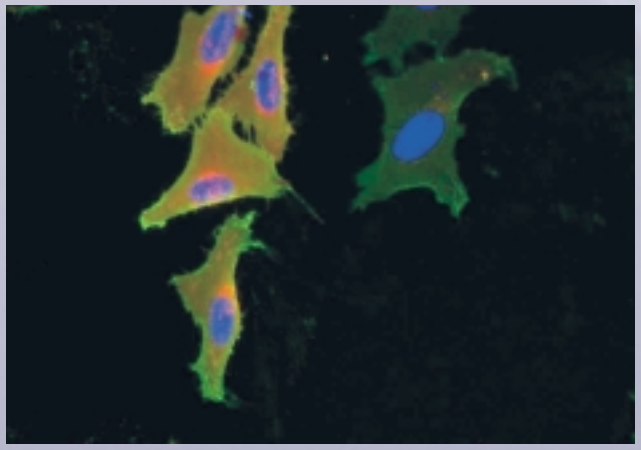


Fig. 1:
Cell nucleus (blue), viral protein in endoplasmatic reticulum (red), viral protein on cell surface (green).
Photo: *Urban Liebel*, EMBL Heidelberg.

The goal of drug research

One of the most impressive examples illustrating the efficiency of automated analyzing systems is the decoding of the human genome in the past decade. Today, the complete list of all genes and proteins making up the biology of man are available to medical research. It must be said, however, that this list gives little or no indication as to which protein needs to be modulated to be able to treat a disease. It is only the understanding of the functioning of a specific gene or protein and the explanation of the molecular interaction on which the disease is based or by which it is caused that leads to the identification of a potential drug. The protein associated with the disease is called the target molecule or drug target. The first critical step in researching into a new drug is the identification and evaluation of a specific, pharmaceutically relevant protein. Researchers are aiming at modulating this protein in order to treat the disease in question.

Modern chemistry in Medicine

In recent years, the methodology of medical chemistry has also changed. Formerly, chemists synthesized relatively large quantities of pure substances which were then tested in complex and sophisticated biological systems. The combination of synthetic chemistry, automation and data processing has given rise to a new approach in medical chemistry: the diversity of synthesized compounds is more important than their quantity. New, parallel syntheses and the combinatorics provided by modern chemistry create new, multi-faceted substance libraries of potential drugs.

Analysis of microscopically small samples

Screening is the first stage in the discovery process for a new drug. It stands for the automatic investigation and testing of the activity of chemically synthesized molecules in biological microsamples. The examined samples may be of a totally different nature and origin. Normally they consist of protein solutions containing the target molecule. However, they may also be specific cell lines that produce the target molecule to be examined. The analysis of molecular interaction in the biological sample is performed by means of an optical signal whose properties depend on the molecular binding status of the examined sample. The analyzed parameters include, for example, absorption, intensity of fluorescence, polarization, or the time-resolved fluorescence in a test volume of a few microliters.

Parallel processing provides high throughput rates

As the chemical substance libraries to be tested consist of several hundred thousand or even millions of different compounds, the screening of the complete library can only be achieved within a few days or weeks by per-

forming the analyses in parallel steps. Present-day screening systems with high and ultra-high throughput rates, so-called High Throughput- and Ultra High Throughput Systems, analyze the biological samples fully automatically in microtiter plates with 384 or 1536 sample wells. Each sample well contains only a few microliters of the specimen to be examined. During the screening process, liquid handling stations add different reagents at precisely defined intervals in precisely defined microvolumes to the individual sample wells. The optical reader of the screening system measures and records the molecular interaction between the test substances and the target molecule. To make sure that every test sample is evaluated according to the same analyzing protocol, liquid handling and optical readout in all sample wells must be exactly synchronized. Powerful, state-of-the-art process software takes care of the entire process control – from the handling of microtiter plates to data acquisition.

For years, research teams of Hoffmann-La Roche and Carl Zeiss have closely cooperated in the development of an integrated hardware and software platform for Ultra High Throughput Screening. The result is the **plate::explorer®** – a real all-rounder in pharmaceutical drug research. With the high-precision analyzer **plate::vision®** integrated into the screening system, researchers have succeeded for the very first time in providing a fully automatic analysis of the time behavior of the molecular interaction between a target molecule and the synthesized substances at a throughput rate of 100,000 samples per day.

Secondary screening of molecular affinities

The active substances identified in a screening process are denoted as "hits". They are the basis for further, more refined analyzing processes. The next step in the discovery process is called secondary screening and consists of the precise investigation and confirmation of the interaction of the target molecule with the hit identified in primary screening. Here, the molecular affinity between the target molecule and the synthesized, active substances is precisely analyzed and quantified in a series of tests under biological conditions. Qualitative and quantitative information on the interaction between the examined target molecule and the hit identified in screening is the basis for a refined chemical synthesis program that will culminate in a promising drug to be tested in clinical trials.

Screening of cells – the challenge of the future

In today's High Throughput Screening methods an average value from several hundred to thousand cells is obtained of the optical signals measured on the cells. In High Throughput Screening it is not yet possible to achieve analyses of cellular resolution. Optical measurement is performed by calculating a mean value for a large number of cells in the wells of the microtiter plate. If the molecular interaction in the cell fails to lead to a macroscopic optical signal, the interaction between the target and the examined molecule will remain undiscovered.

The future enhancement of High Content Screening methods based on individual cells for the detailed investigation of molecular activity at a cellular or subcellular level is the most fascinating technical and scientific challenge in modern microscopy today.

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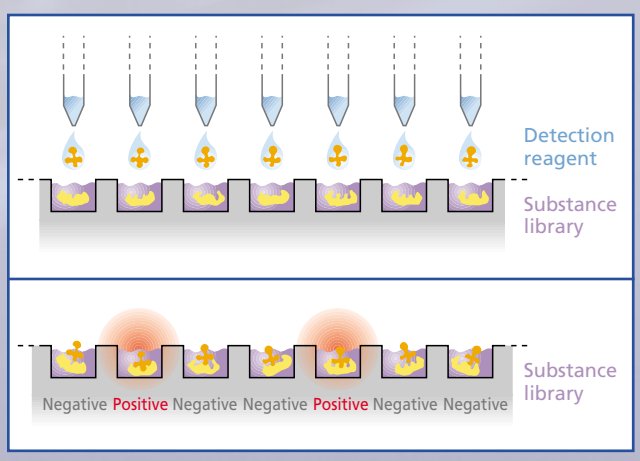
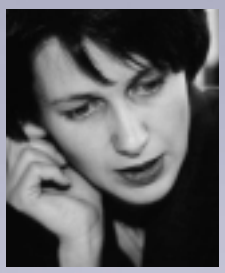


Fig. 2: Screening – systematic analysis of molecular affinities in substance libraries, UHTS principle.

plate::vision® – The System of Many Talents

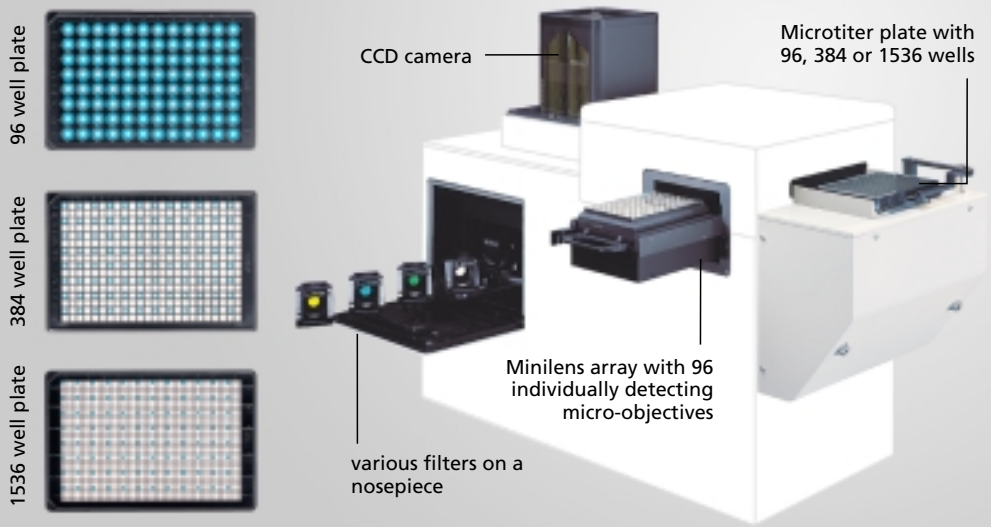


Anke Biester

In the field of medicine, the process of discovering new drugs is extremely costly and time-consuming. A potential candidate drug has to go through countless tests before it can be used in initial patient trials. This not only costs money, but above all, time. For this reason, one of the top priorities for scientists is to find possible ways to accelerate these processes. In the past, standardized measuring devices were used. These either measured with a high degree of accuracy but little speed, or were very fast but lacked precision. The new reader from Carl Zeiss is not only fast and accurate with small sample volumes, but also offers the user all kinds of possibilities for varying research methods.

Finding a new active principle for a drug is like searching for a needle in a haystack: between 500,000 and a million chemical compounds have now been recorded in substance libraries. Searching through all of these substances for a potential candidate drug for a therapeutic target molecule costs both time and money. First of all, this huge range of substances has to go through numerous series of tests, and a few selected substances are then put onto a short list. Typically only 0.1% of the substance library passes the initial search test. These substances then form the subject of further research and optimization. Of the six to ten substances that eventually go through clinical trials, often only one will be successful. This means that a million or more substances have to be tested to discover just one drug. The aim, therefore, has to be to optimize this process, or in other words to perform these series of tests as quickly as possible and with the lowest achievable levels of reagents and consumables. Biochemical detection reactions, so-called assays, are developed for this purpose. These convert a specific biochemical property of a therapeutic target molecule into an optically detectable signal, which is measured using standardized procedures. Here researchers use what are known as microtiter plates, which contain numerous small reaction chambers (wells). Their development mirrors the miniaturization of chips in the computer industry: the number of wells on the plates is increasing all the time, whilst their volume is getting smaller and smaller. Plates with 384 wells and a volume of 50 microliters per well have now become standard. However, 1536-well plates with volumes of between five and ten microliters per well are also available. As they allow a high sample throughput, such procedures are known as Ultra High Throughput Screening.

plate::vision® Reader



Miniaturization just like the computer industry

This miniaturization not only saves time, it also saves money: using the old 96-well plates with volumes of 250 microliters, the pharmaceutical industry incurred costs of around ten million US dollars in 1998 to test a million samples. With the new 1536-well plates, on the other hand, this falls to around 0.5 million US dollars.

Miniaturization alone, however, is not the answer. In the past it simply took too long to measure samples with sufficient precision. Each sample on the microtiter plate had to be measured individually. With 1536 samples on a plate this took around fifteen to thirty minutes; furthermore, no kinetic data could be collected.

Performing rapid measurements, though, meant sacrificing quality: the entire plate with all the samples was exposed at the same time. Although this is an extremely fast method, and also suitable for kinetic measurements, it is not very accurate due to effects such as scattered light from neighboring samples.

Speed and quality guaranteed

The **plate::vision®** multimode reader offers both speed and quality. It is fast and accurate, as it works with a miniature lens array of 96 micro-objectives, allowing 96 wells to be detected in parallel. These 96 micro-optics guarantee highly accurate, sensitive measurements and synchronous handling of the samples. A 96-well plate is measured in a single step, which takes no longer than a second. A 1536-sample plate requires 16 steps, taking less than 30 seconds in total. This means that hundreds of thousands of samples can be tested on a daily basis.

What is unique about the development of the **plate::vision®** is the close collaboration between Roche and Carl Zeiss (see also interview below). As potential users, Roche's researchers were able to guide the development of the reader and thereby realize most of their ideas. The result is an easy-to-operate, multifunctional instrument, which, in the opinion of its users, is exceptional in terms of both speed and accuracy.

Introducing a system of many talents

The compact design of the reader was achieved using a folded beam path, similar to that of an inverted microscope. With the help of a dichroic mirror, excitation and detection can take place in the same beam path. Not only are the filters for the measurements – there are several filters on a filter revolver – exchangeable in one operation, but the system is also compatible with the most commonly used filters, i.e. it is not tied to a specific filter manufacturer. The miniature lens array itself, consisting of 96 small objectives, is geared to the measurement mode in question and can be exchanged in a single operation. Absorption, for example, is measured using miniature lenses with very narrow foci. This prevents the meniscus of the sample liquid from disrupting the measurement. Fluorescence and luminescence, on the other hand, are measured using miniature lenses with quasi-confocal detection. Here the detection volume is in the region of ten nanoliters. Effects such as autofluorescence, crosstalk (beams from neighboring samples) or scattered light are avoided. The **plate::vision®** reader can be used to measure absorption, fluorescence, luminescence and now also fluorescence polarization and time resolved fluorescence. This last procedure replaces numerous tests with radioactive material.

To further simplify series of tests, a workstation surrounds the **plate::vision®**. The individual processing instruments are arranged around rotary tables, which make bi-directional and parallel plate transport to all instruments possible, in the sequence specified by the user in the software. Several series of tests can therefore be performed fully automatically.

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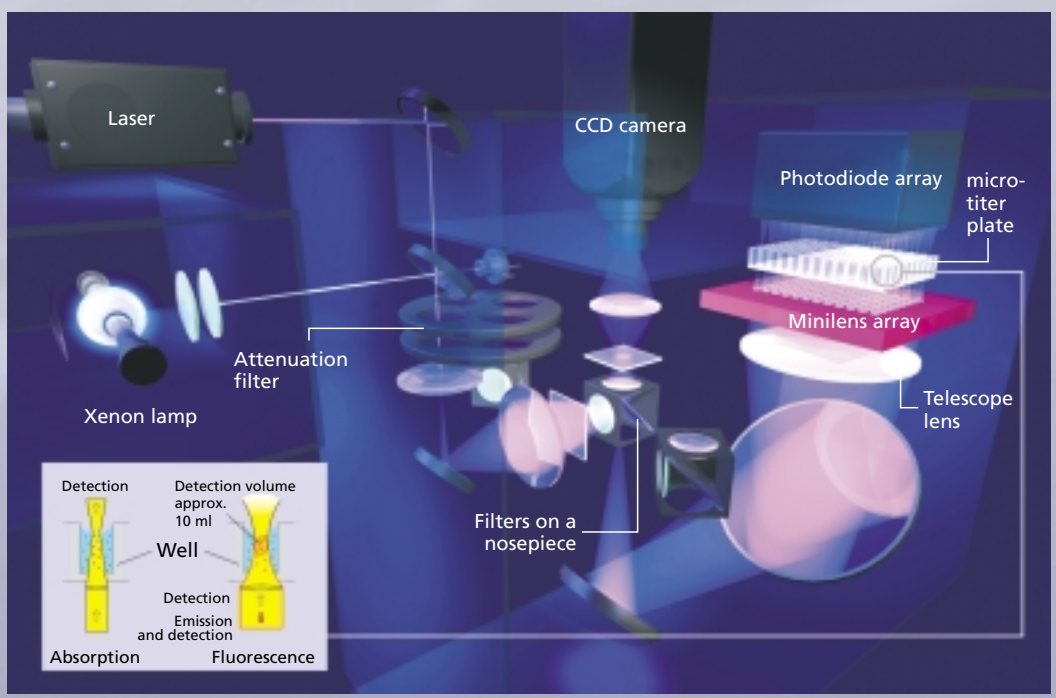

Fig. 1:
The modular design of the **plate::vision®** reader allows the use of optimum measurement parameters: the filters, miniature lens array and detection camera can be changed easily as required.

Fig. 2:
Inside a **plate::vision®** reader: the exchangeable miniature lens array ensures the optimum focus for both absorption and fluorescence measurements (very narrow focus or detection volume around 10 nl).

We Don't Compromise in Screening

Dr. Thilo Enderle **works at the Assay Development and High Throughput Screening Department of Roche Pharmaceuticals in Basel. He was responsible for the development of the plate::vision® at Roche and coordinated the installation of the newly developed instruments at six Roche research locations worldwide.**
Anke Biester **interviewed** ***Dr. Enderle*****.**

What do you like about the ***plate::vision®****?*

The reader offers a well-balanced combination of the essential factors, such as sensitivity, flexibility, maximum throughput and user-friendly operation. Certain specialized instruments are slightly better on one specific factor, such as sensitivity for luminescence, but no other device has been so well optimized for a wide range of applications. The reader from Zeiss meets the demands of Ultra High Throughput Screening, within the bounds of what is technically possible.

Could you say that the ***plate::vision®*** *reader is what every researcher has been waiting for – an instrument that offers excellence in every area?*

Yes, you could certainly see it like that.

What was collaborating with Carl Zeiss like?

It was very interesting, as essentially two very different worlds were brought together: Zeiss specializes in metrology, microscopy, optical design, etc., while Roche presented a wide range of requirements within the field of pharmaceutical research and an in-depth knowledge of the tasks that need to be mastered in the drug discovery process. For our researchers, participating in the development process was an opportunity to build an instrument that was tailored to their requirements, rather than buying one that had already been manufactured. This meant that instead of having to tailor their tests to an instrument, they had the chance to mold an instrument to meet their various needs and make the things that other instruments could not offer a reality.

What steps were needed in the development process?

First we had to find a common language. A word that means one thing to a biologist can mean something quite different to a technician. We formulated requirements and specifications at Roche. The developers at Zeiss then told us what was possible and made suggestions, which we then analyzed to determine their applicability within research. Finally, Zeiss transformed the solutions we had worked out together into a quality product.

Was it clear from the beginning that you would use the instruments?

No, we had an open mind about it. Initially we were only thinking about installing an instrument in Basel. But when the prototype was presented, everyone was full of enthusiasm. We then decided to equip all of our research locations with a screening system and a common platform. And the **plate::vision®** reader, including software, was ideal for this.

What was it that convinced Roche?

On the one hand, of course, the excellent results achieved with the instrument. But the successful collaboration with Zeiss also impressed many people. The **plate::vision®** covers the high demands of pharmaceutical research to optimum effect. The common platform also enables us to exchange our experiences with the instrument and with series of measurements on an international scale within the company. This will allow us to learn together within our global network and build up a huge body of knowledge. Communication will also become more transparent if we are working with the same kinds of instrument.

*Are any improvements still to be made to the **plate::vision**®?*

You can of course always make further improvements to any instrument. We have now added fluorescence polarization and time resolved fluorescence. The latter, due to the high sensitivity of the detection, replaces the numerous tests that would otherwise have to be performed with radioactive material. The modular design of the reader has proven to be a major advantage for these upgrades: they can be done at comparatively little cost.

The development of microtiter plates is often compared with that of computer chips. Will miniaturization soon reach its limit in this area too?

With the new Zeiss reader we could reduce the sample volume to less than ten nanoliters with no loss of sensitivity, as that is currently the detection volume. The limiting factor will be our ability to handle liquids in the sample plates. I think that the aim for the next few years will be to get the 1536-well plates fully established. With these we are already talking about a sample volume of no more than a few millionths of a liter. Any further miniaturization would make it difficult to handle liquids in such small volumes. In such cases, for cell-based measurements, there would be only a few hundred cells in the sample. This would soon raise the problem of the statistical relevance of such a test – not to mention the difficulties involved in actually getting the cells into the samples in exact quantities or cultivating them in such small volumes of liquid. Miniaturization must make sense. We don't need some fancy hitech toy, but rather innovations that actually take us forward. At the end of the day, the task of pharmaceutical research is to discover new drugs, not to possess new technologies. We have to ask ourselves the question: "Does a new technology help us master our tasks more effectively, or does it solve a problem that we don't even have?"

The fact that we are now able to master our tasks more effectively is down to Zeiss and the **plate::vision**®. "We don't compromise in screening…"

Dr. Thilo Enderle, Assay Development and High Throughput Screening, F. Hoffmann-La Roche, Roche Pharmaceuticals, Basel
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Fig. 1:
The **plate::vision**® reader is the centerpiece of the modular UHTS system from Carl Zeiss, which is in use at all F. Hoffmann-La Roche research locations. The UHTS system can be configured with a variety of modules, such as reader workstation, liquid handling workstation or hotel workstation.

Molecular Methods In Clinical Diagnosis Mo

Georgia Lahr

Ever since the human genome has been decoded, biotechnology and genetic engineering have been major topics in the media. The subject matters range from DNA diagnosis to stem cell therapy. These terms stand for different test procedures with special clinical indications. The analysis of genes permits the detection of certain diseases or predispositions, since many of these are genetically caused.

Early diagnosis of diseases

The human genome, a perfect construction manual for the organism, was decoded only recently. However, the comprehensive analysis of genome functions has largely remained unsuccessful, i.e. there is barely anything known about the complex path between instructions and organism. Even the replacement of a single base within the human genome, called point mutation, can lead to diseases. Here, molecular diagnostics will be a major provider of information to medicine in the future. If a modified gene or DNA sequence is identified early enough, therapies having a positive influence on the course of the disease can be started in good time and markedly increase the chances of recovery.

Mutations made visible

To some extent, the causes of cancer have been investigated very well. One example of this is the development of colon cancer. In industrialized countries, colon cancer numbers among the most frequent new malignant diseases. At first, a glandular cell in the intestinal wall turns into a benign tumor (adenoma), for example by mutation, which later changes into a malign tumor (carcinoma), because of further genetic mutations in the DNA. These mutations result in a carcinogenic effect on the K-ras oncogene and reduce the carcinostatic effect of the DCC and p53 tumor suppressor genes. The development from adenoma to carcinoma often takes more than 10 years and is directly related to the quantity of poisonous substances that come into contact with the intestinal cell in the

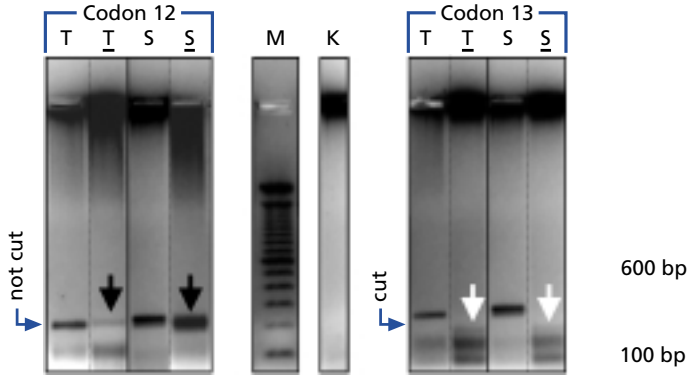


Fig. 2:
Electrophoresic separation of DNA fragments on an agarose gel. This concerns the mutation analysis of an intestinal cancer tissue specimen. The hereditary material (DNA) was isolated and multiplied via PCR. The "multiplied" DNA is made visible in the gel by labeling it with ethidium bromide. The left side shows the restriction analysis for mutation in codon 12 of the K-ras gene. The right side shows the codon 13 analysis of the same gene. This analysis clearly shows that codon 12 of the K-ras gene in the patient DNA (T) is mutated (not cut), while the following codon 13 is available as a wild-type sequence, since it has been cut.

ving Ahead

Fig. 1:
The hereditary substance (DNA) consists of four bases: adenine (red), guanine (green), cytosine (blue) and thymine (yellow).

course of its existence. Molecular methods permit these changes or mutations, such as the aforesaid K-ras gene mutation, to be detected through gene analyses. These sensitive methods of analyzing the DNA structure are often based on the polymerase chain reaction (PCR). This examination technique requires the hereditary material to be isolated from the examination material concerned (biopsy, bone marrow aspirate, blood, mucosal smear). The PCR technique will then multiply the hereditary material isolated from a few cells to such an extent that it can be analyzed. After this, agarose gel electrophoresis permits the reaction products to be separated according to size (Fig. 2). After an electric field has been applied, short DNA fragments move through the agarose matrix faster than long fragments. After specific dyeing, the fragments become visible in the gel. For orientation purposes, a so-called size standard is used, which shows, for example, all the 100 base pairs of a band in the gel (100 bp ladder) (Fig. 2, track M).

After multiplying, the resulting PCR reaction products can be examined more precisely for mutations in complex analysis procedures. This is now done frequently via automatic sequencing of the multiplied PCR fragments or via following enzymatic reactions (e. g. restriction analysis).

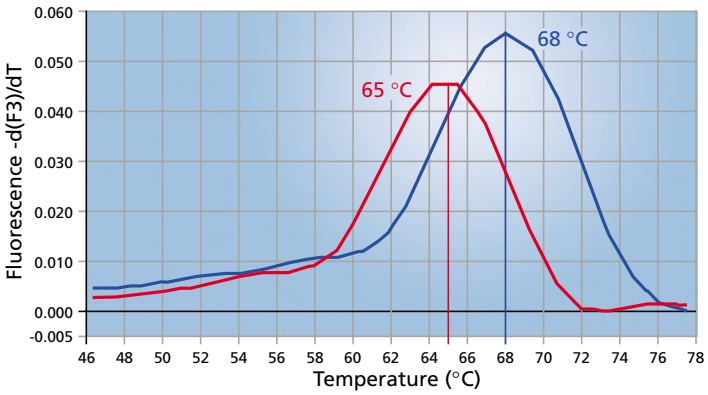
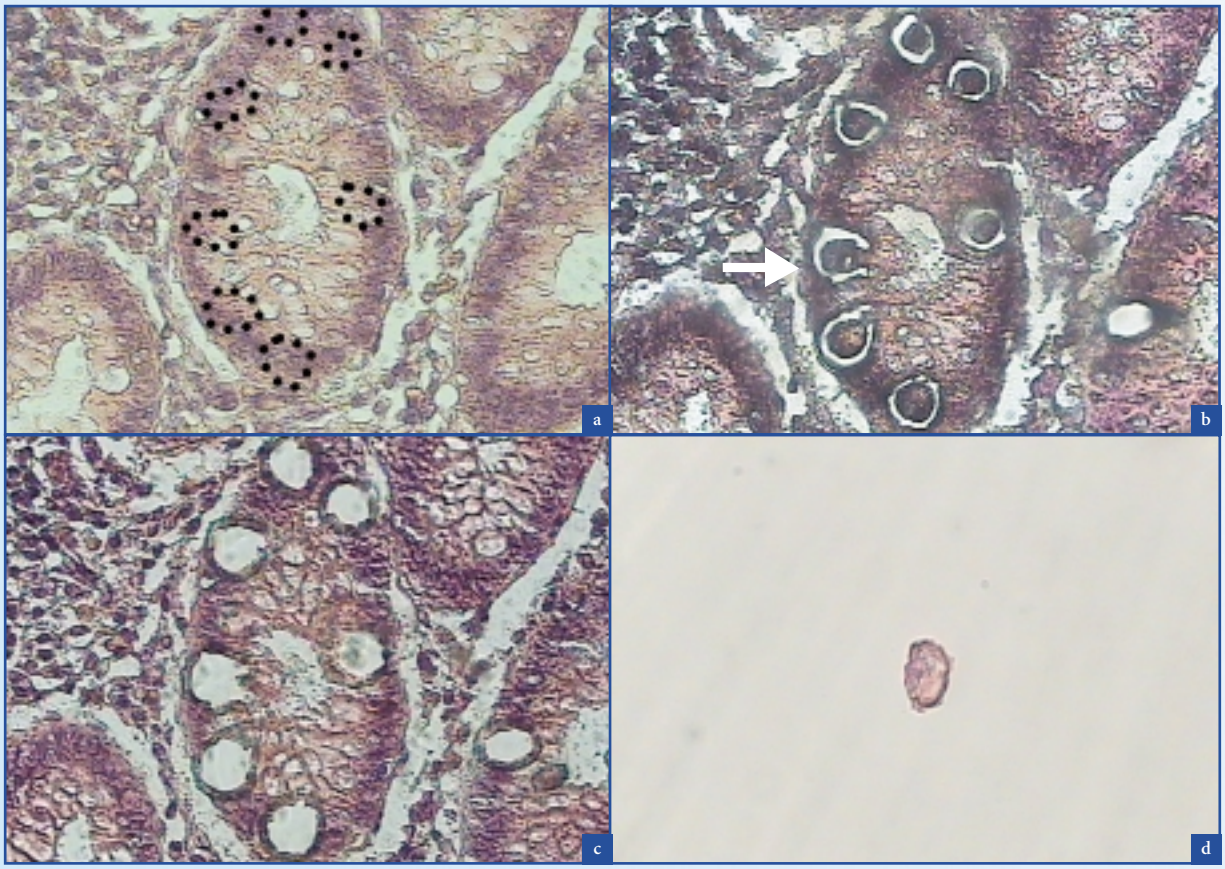


Fig. 3:
Data analysis of the K-ras LightCyler PCR: healthy wild-type DNA (blue), mutated DNA (red). Both DNAs originate in tumor cell lines. The SW-480 cell line (red) includes a familiar mutation in codon 12 and features a melting temperature of 65 °C, while the melting temperature of the healthy wild-type DNA (blue) is 68 °C. These differences make it possible to clearly identify the codon 12 mutation in the K-ras gene.

Molecular "scissors" (restriction enzymes) cut the PCR fragments at a specific site, e. g. if the unmodified wild type sequence is available. However, if the DNA features a mutation, the PCR fragments will not be cut. Such a K-ras restriction analysis is shown in Fig. 2. Today it is possible, however, to analyze known point mutations in a "disease gene" more quickly using the LightCycler technique. This technique not only multiplies the DNA, but also permits direct evaluation through continuous measurement of the reaction products (key word: real-time PCR). The application of one or several laser-sensitive dyes enables detection of successful multiplying "in solution", i. e. without an additional step such as gel electrophoresis. Sequence deviations, for example point mutations, can also be detected "in solution" using melting point analysis (Fig. 3), due to which the very expensive and time-consuming sequencing or restriction analysis of the PCR reaction products (see above) is no longer required. The benefits of the LightCycler technique are its great speed, reproducibility and nonexistence of contamination problems, i. e. urgently required examination results can be provided quickly.

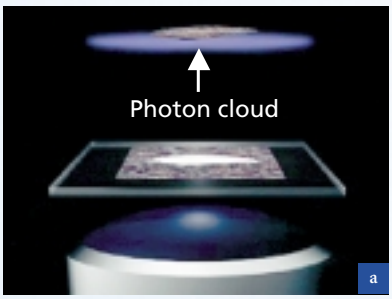


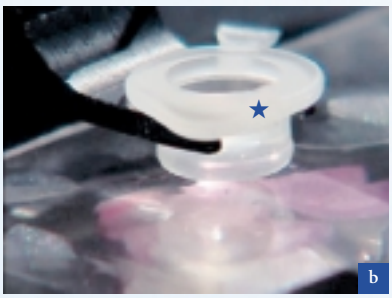
Figs 4a to 4d:
Micrographs of the laser scalpel/catapult technology for the isolation of single cells from a tissue section. (a) Tissue section before laser microdissection. (b) After laser microdissection of cells; clearly recognizable by the gap (white arrow) in the tissue section. (c) The remaining tissue after cell catapulting. (d) One of the catapulted cells in the receiving vessel.

Obtaining homogeneous specimens

Molecular examination methods require very pure specimens. The more precisely cells can be isolated from morphologically defined areas, the more precise the information that can be obtained about the status of a disease, for example. This requires the tissue, taken from a colonoscopy, for example, to be fixed (preserved), cut in extremely thin slices using a microtome, and mounted on an object carrier (Fig. 4a). The sections can then be further processed with the standard dyeing techniques used in histology (e. g. hematoxyline-eosin) to facilitate identification and observation under the microscope. Laser microdissection allows single specific cells to be isolated from such histological sections. The laser scalpel/catapult technique used for this purpose permits the cells to be both cut (Fig. 4b) and transported merely by means of laser light (Fig. 5). The cell material is transferred into a receiving vessel (Fig. 4d) in a contact-free and contamination-free manner. The laser beam, generated by a pulsed nitrogen laser with a wavelength of 337 nanometers (UV-A), is mirrored into the beam path of a standard research microscope. The optical system focuses it on a focal spot – not even one micrometer in diameter – in the plane of the viewed object. The beam "cuts" finest gaps into the biological material, because an extremely large number of photons impinge on the molecules within three nanoseconds, thus breaking the chemical bonds. This process is called photo decomposition. Both the isolated cells themselves and the surrounding regions remain intact. A further short laser pulse of three nanoseconds then safely catapults the "freed" cells from the object carrier into a receiving vessel several millimeters away within fractions of a second (Fig. 5). The cells cut out are virtually flung out by the slightly widened laser beam. Further molecular-biological examinations, for example for mutations in the K-ras gene, can then be performed without any restrictions (Figs 2 and 3).

Even if the complete cure of recognized gene defects is not yet possible, an early diagnosis at least provides the chance that, in many cases, expected secondary damage can be avoided or at least minimized by suitable measures being taken early enough. As a preventive medical measure, molecular diagnosis has interesting aspects both for patients and the economy. A small tissue specimen might one day be sufficient to detect mRNA expression patterns and protein patterns that perhaps already show the beginnings of a tumor cell.





Figs 5a and 5b:
Catapulting process using the laser scalpel/catapult: the microscope optics focuses the laser beam in the plane of the viewed object. The laser beam cuts a cell area out of a histological tissue section. A short laser pulse then catapults these "freed" cells out of the object carrier on a "photon cloud", against gravity, over a distance of several millimeters. These cells can be captured in the cover (asterisk) of a centrifuge tube positioned exactly above the section and then subjected to molecular-biological examination (b).

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glossary

Amino acid
Organic, nitrogen-containing molecules which serve as proteins.

DNA
Deoxyribonucleic acid. The material of which genes are made. Hereditary material of all living creatures in the nucleus of each cell. If the entire DNA of a human cell were linearized, it would measure approx. 2 meters. DNA consists of approximately six billion individual components.

DNA fragment
Fragment of a DNA strand containing a number of nucleotides. DNA fragments are generated when, for example, a strand is divided by restriction enzymes.

Enzymes
are proteins which speed up biochemical reactions in the cell metabolism. Only the activities of enzymes permit a proper metabolism.

Gel electrophoresis
Biochemical analysis technique where organic compounds with dipole features are separated in the electric field due to their different migration speeds.

Gene
Unit of hereditary information, where the amino acid sequence of one protein or one RNA is coded. Humans have approximately 50,000 different genes.

Gene technology
Methods for the characterization, isolation and recombination of genetic material based on molecular-biological discoveries.

Gene therapy
Experimental type of therapy which tries to influence the course of the disease on a molecular level by adding new genes or replacing defective ones.

Genetic code
Coding of hereditary information via a defined sequence of bases.

Messenger RNA (mRNA)
Single-stranded nucleic acid formed in the cell nucleus complementary to one strand of DNA double helix.

Molecular biology
Science of the effects and regularities of life processes on a molecular level.

Mutations
Changes in the genome caused by spontaneous events or triggered by mutagens such as UV light and chemicals.

Nucleotide
Single component of DNA or RNA.

Oncogene
A gene which takes an active part in the conversion of a body cell to a tumor cell.

PCR
Polymerase Chain Reaction. Fundamental technology for the fast multiplying of certain RNA or DNA regions.

Ras gene
Proto-oncogene
(abbreviation of "rat sarcoma")

Restriction enzyme, restriction endonuclease
Enzyme that cuts DNA molecules at a specific nucleotide sequence.

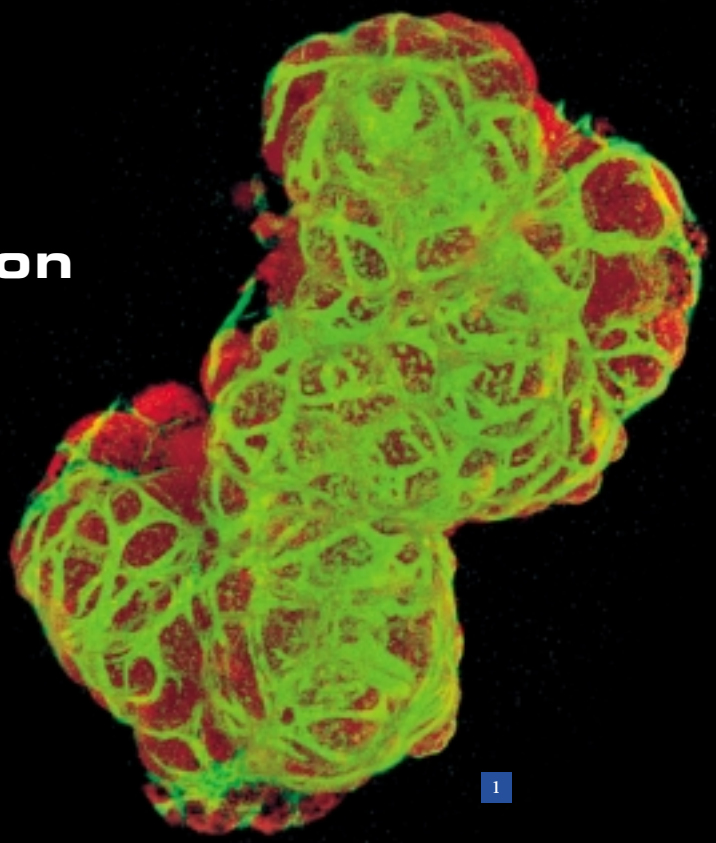
Tumor suppressor gene
Gene that prevents the conversion of body cells in tumor cells.

Sequencing
Determination of the base sequence of a DNA or RNA strand and the amino acid sequence of a protein.

Stem cell
Pluripotent mother cell, origin of all blood cells.

Wild type
Original form of a gene or organism which has been modified neither by breeding nor by genetic engineering.

Cells Under Observation



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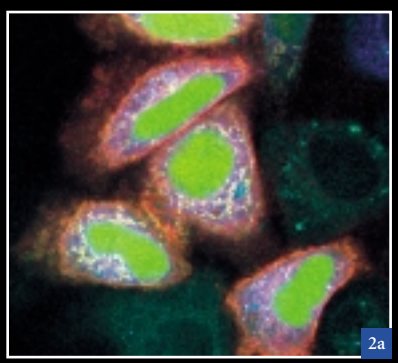
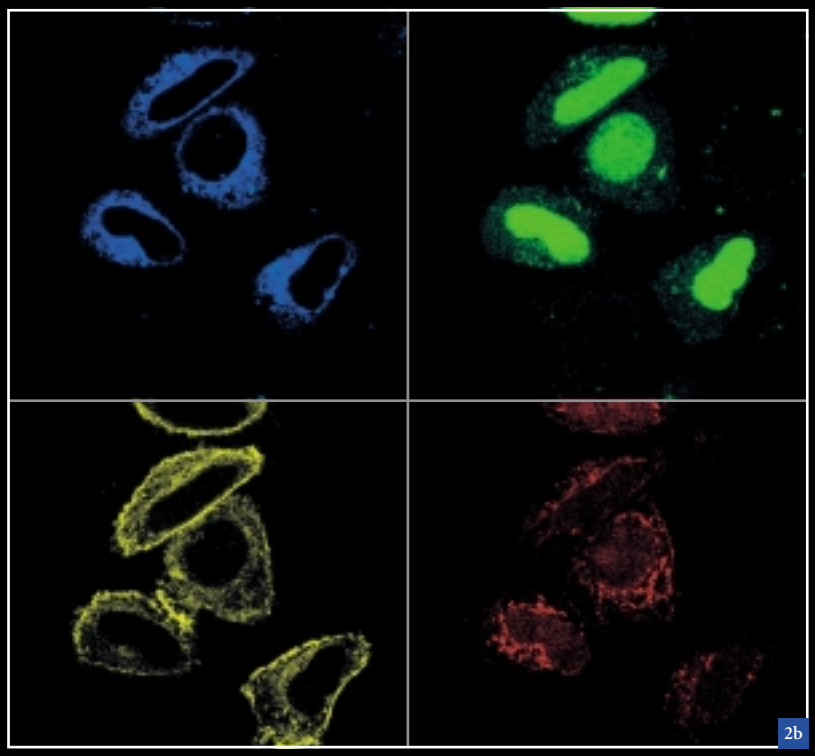
Cancer is the second most frequent cause of death worldwide. In Germany alone, there are approx. 340,000 new cases and 220,000 deaths every year. And medicine is still unable in many cases to fight cancer with a therapy promising complete recovery. Traditional treatment (surgery, radiotherapy, chemotherapy) aimed at removing the diseased tissue or preventing its reformation is unfortunately not always successful. It would be much better if the causes of cancer growth were known and could be fought in the early stage of the disease.

The best known triggers of uncontrolled cell division and carcinoma formation, generally described as cancer, are genetic modifications of the cells concerned. As a result, the communication between protein molecules controlling processes in the cell – particularly the cell division – is disturbed.



2a



2b

Fine details are recognized

Laser scanning microscopes are used in cancer research laboratories for the direct visualization of protein molecules in the cell playing a part in carcinoma formation. For this purpose, every structure to be examined is labeled with a special dye probe which makes it possible to identify and follow the structure. However, existing conventional laser scanning microscopes reach their limits where the examination of regulation networks involved in cancer formation is concerned. They permit the reliable detection and simultaneous observation of only a few of the many proteins involved in wrong programming. This means prolonged series of experiments and uncertainties in evaluation.

META follows proteins going astray

The **LSM 510 META** laser scanning microscope developed by Carl Zeiss in cooperation with the California Institute of Technology in Pasadena, USA, puts an end to this restriction. A new detection technique, which combines modern measuring technology with intelligent software, permits the existence and distribution of far more structures and protein molecules in the living cancer cell than ever before to be observed simultaneously and their behavior in the course of time to be visualized. Where several proteins are "suspicious", it is possible to see all of them at a single glance. The fact that the differentiation of very similar dyes is no problem for the **META** is a new feature. This increases the number of usable dyes and – since not every dye is equally suitable for every protein – also the number of options. Therefore, the new technique permits entirely new experimental approaches which make commenting on the molecular causes of tumor formation and behavior much quicker and more precise.

The preparation of new, promising therapies for cancer diseases is only one example for the versatile applications of the **LSM 510 META** from Carl Zeiss. This laser scanning microscope for biomedical research launched one year ago was received very positively on the market. It recently received the R&D 100 Award from the US American R&D Magazine. Every year, this prize is awarded to the 100 best technical developments worldwide.

Figs 1a and 1b:
The LSM 510 META laser scanning microscope permits the examination of fine structures of cells and tissues with high 3-dimensional resolution. Biopsy specimen from the salivary gland of a mouse in 3D projection.
The modular design of the LSM 510 META provides the user with uncompromising flexibility.

Figs 2a and 2b:
Faster progress in experimental cancer research due to the safe identification of several proteins observed simultaneously: tumor cells in cell culture marked with four different dyes.
2a and 2b: laser scanning micrograph after detection of the dyes using the LSM 510 META.
Specimen: *Dr. A. Miyawaki*, RIKEN, Japan.

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Steel In Focus

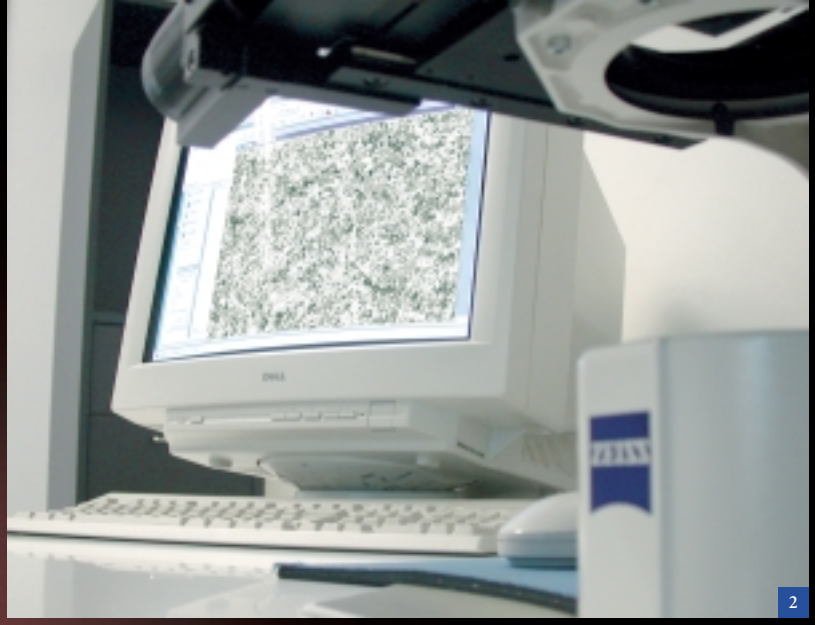
Karl Hübner

Producers of steel must be careful about many things: the correct dosage of alloying materials, for example. Or the optimum cool-down speed to ensure that the product solidifies in the required way. Some laboratory tasks require monitoring through the microscope. The Swiss company von Moos Stahl has been using the Axioplan® 2 from Carl Zeiss for this purpose for three years now.

The Lucerne canoe club calls the "Kleine Emme" river its "Hausbach", i. e. its very own "local stream", and recommends it to all those canoeists "who don't like it too wild". In June 1996, however, the longest river in the Swiss Canton of Lucerne turned out to be quite different. The photos of the turbulent meltwater floods can still be found in the Internet.

In turbulent waters

Did nature just want to provide the suitable setting for the events in the Swiss steel industry in that year? Since time immemorial, the Kleine Emme has led its waters to Emmenbrücke before flowing into the Reuss. Here, on the left bank of the river, von Moos Stahl – a family-owned company – has produced steel since 1842. Until 1996.



Then the Swiss steel companies were restructured. These were turbulent times, at the end of which von Moos Stahl was merged into the new Swiss Steel AG. The results: reorganization and streamlining of the portfolio. However, the name has remained. With its know-how of over 150 years, von Moos is now concentrating on high-grade, bright and free-cutting steels. Though under a new roof, steel is still being produced in Emmenbrücke; the Kleine Emme has calmed down again.

Today, the company produces more than 400,000 tons of steel every year; about 200 types for more than 250 customers. The major customers are car manufacturers and their suppliers, and manufacturers of plants and machines – mainly in Switzerland, Germany, Italy and France.

Quality assurance in microscopic detail

The quality is monitored by a staff of about two dozen. The spectroscopy laboratory monitors the precise dosage of alloying materials in various molten steels. The solidity laboratory examines mechanical properties, tensile strength, for example. The biggest laboratory, however, deals with metallography. Here, production samples as broad as a finger are ground, finely polished using a diamond suspension, and then examined under the microscope.

The spick-and-span samples are placed on the object stage of a microscope – the **Axioplan® 2** from Carl Zeiss. Normally, a magnification of 50x is sufficient to turn the polished and apparently very uniform surface of the steel into one of blemishes. Small, long drawn-out capsules appear on the bright background. Metallographers call them non-metallic inclusions (NMI). "Oxides, sulfides and silicates," explains Odette Lötscher, metallography expert at von Moos Stahl.

These unwanted, microscopic NMIs are inherent in production. Oxides and silicates make steel brittle and constitute internal notches which can result in failure of the finished steel components in the case of high strain. Therefore, determination of the degree of oxidic purity prior to further use of the steel is of major importance. This is what is done in metallography.

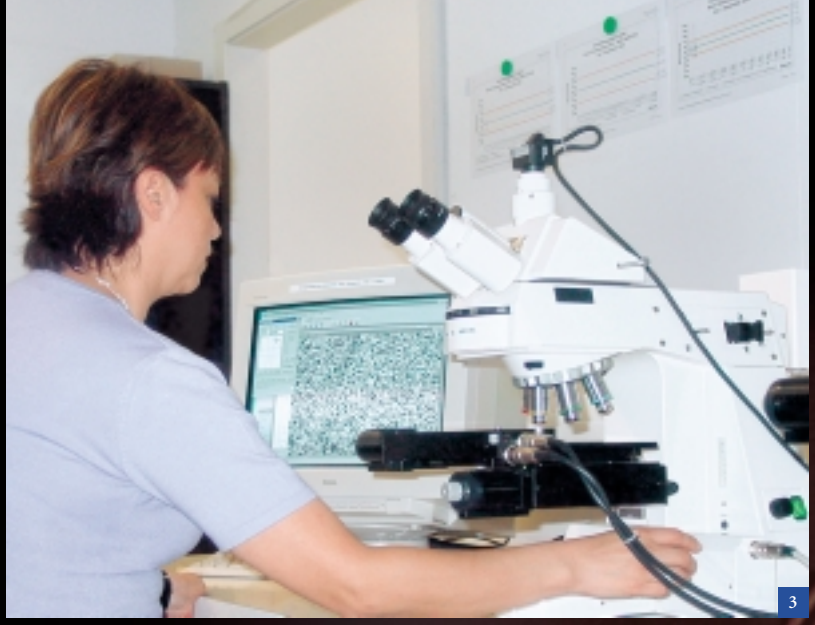
Sulfide inclusions are less problematic. They are softer and accommodate to deformation more easily. For the production of free-cutting steels, a defined portion of manganese sulfide is even desired, since this improves the machining properties of the steel.

Software with measuring eyes

Due to their great influence on steel properties, the determination of NMIs is a major routine check in the steel laboratory. Trained eyes like those of Odette Lötscher immediately recognize the difference between oxides and sulfides under the microscope. "The color makes the difference. Oxides are black, sulfides gray." However, not only the type and quantity of NMIs are important for assessment,

Fig. 1 (background):
Iron annealing. At first, the Swiss steel producers melt iron scrap in the electric arc furnace. The glowing liquid iron is the starting point of high-grade steel products.

Fig. 2:
Etched steel magnified 100x. The black-and-white areas provide information about the perlite-ferrite distribution in the steel.



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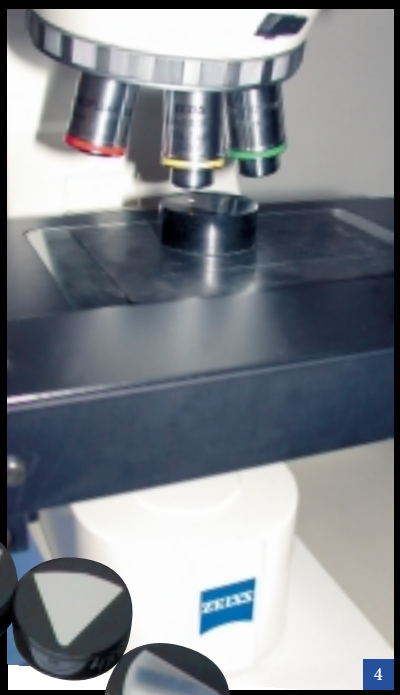

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5

but also their size. The bigger the inclusions, the more they affect the crystal structure of the steel – and therefore its properties.

Ever since the von Moos laboratory has used **Axioplan® 2** microscopes, *Ms Lötscher* only needs to look through the eyepiece for control purposes. As soon as she has placed the polished steel cuboids under the objective, the relevant software, also from Carl Zeiss, does everything else: it controls the microscope, creates the image on the monitor and archives the image data. The KS NMI program specifically detects the data about non-metallic inclusions – not only the total area in square micrometers, but even the distribution of size and type.

The KS 400 software informs *Odette Lötscher* about further parameters which are of interest for quality assessment, like the area distribution of the various perlite and ferrite iron-carbon phases or peripheral decarbonization, i. e. the loss of carbon in the periphery of the steel caused by a high temperature during rolling and the resulting oxidation. The loss of too much carbon will result in hardness reduction at the periphery of the steel.

Although the KS 400 software was mainly designed for image analysis and is not specifically tailored to the requirements of a steel laboratory, an integrated macro editor enables the users to program their own routine procedures for the standardized determination of the parameters which are of interest to them. *Odette Lötscher* has made extensive use of this option and has promptly developed a dozen macros. This not only enables her to determine inclusion areas and decarbonization, but also permits the assessment of grain boundaries, i.e. the border zones between the smallest homogeneous areas in the metal grid, the crystallites.

User requirements welcome

Digital image recording not only offers the benefit of automatic evaluation, but also facilitates archiving of the images needed for documentation purposes. "In the past, one member of the staff took and developed photos practically all day long," remembers *Norbert Gross*, head of the laboratory. And when he says "in the past," he means the time before 1999 – the year in which Zeiss microscopes and digital processing techniques were used for the first time.

Although von Moos Stahl are very satisfied with the Zeiss equipment, they still have a small request: as in every modern laboratory, all the relevant data is combined in a Laboratory Information Management System (LIMS), in this company, too. As regards the data from metallographic microscopy, this is still being done via an intermediary computer – and manually because of the data format. "If Zeiss changed the format, the transfer would be easier to perform," is the wish expressed by von Moos.

This is a request which Carl Zeiss Vision in Hallbergmoos, Germany, has long been ready to meet. Numerous further options have been planned anyway, not only for customers in the steel sector, but for the materials sector in general, where

Zeiss has planned a major campaign. "Many users do not really know that our microscopes can be applied not only in biology and medicine, but also in the materials sector," says *Bruno Linn*, the "materials" project manager. Here he is not only thinking of metallographic applications in the steel, automotive and mechanical engineering sectors, but also of micromechanics and "new materials" such as plasma ceramics and specialty polymers.

In this context, there is also good news for the steel laboratories: in addition to existing special software for NMI examinations, a special grain boundary program will soon be released. Then there would no longer be any need to create a special macro under KS 400. And the data format request from Emmenbrücke will also be met without a lot of water from the Kleine Emme having to flow under the bridge. "This request will be implemented even this year in the next version of our software," announces *Bruno Linn*.

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details

Materials move into focus

In November 2002, Carl Zeiss launched its new line of materials microscopes. Numerous new microscopy solutions have become available to users in materials sciences and analysis. New developments and improvements, based on time-tested solutions from Carl Zeiss for these applications, meet not only the steel manufacturers' requirements.
Both the hardware and the software offer innovative solutions on the basis of high-quality optics combined with new opto-electronic techniques and user-friendly programs.

A number of new techniques also provide options for more efficient and more precise analysis in many applications in the steel industry.

Configurable AxioVision® software
This new image processing and analysis software can be easily tailored to the customers' specific requirements. Easy-to-use "pushbutton solutions" can be created, which provide markedly more efficiency, in particular for routine operation. Special prefabricated application solutions for measurement of the graphite portion, determination of grain sizes and particle analysis support evaluation in compliance with international (ASTM) and DIN standards.

A new DIC technique (DIC = Differential Interference Contrast) enables the user to conveniently image all the available object structures, evaluate them by image analysis and document them.
Numerous objectives, improved in contrast, image quality, edge resolution and homogeneity of the field illumination, form the basis of even more precise evaluation of polished specimens and efficient use in materials analyses.

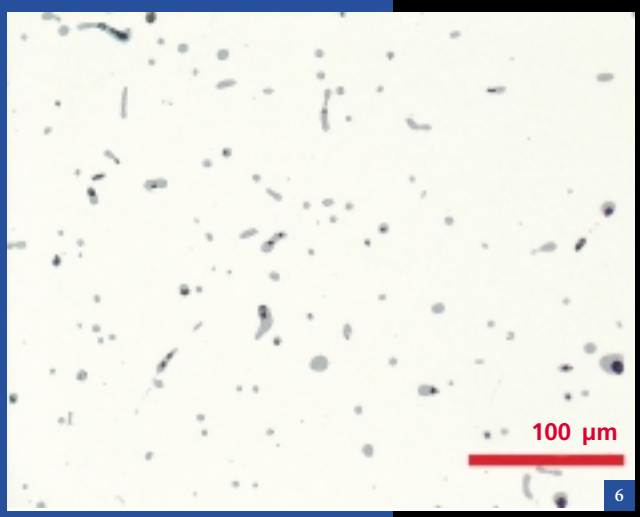


Fig. 3:
Quality inspection using the **Axioplan® 2**. No need to look through the eyepiece, the software calculates the key parameters.

Fig. 4:
Metallic section under the microscope.
Ready for metallography

Fig. 5:
Steel samples – ground, washed and polished.

Fig. 6:
Free-cutting steel containing lead under the microscope. The magnification visualizes the sulfidic inclusions (gray) and also the small lead islands (black).

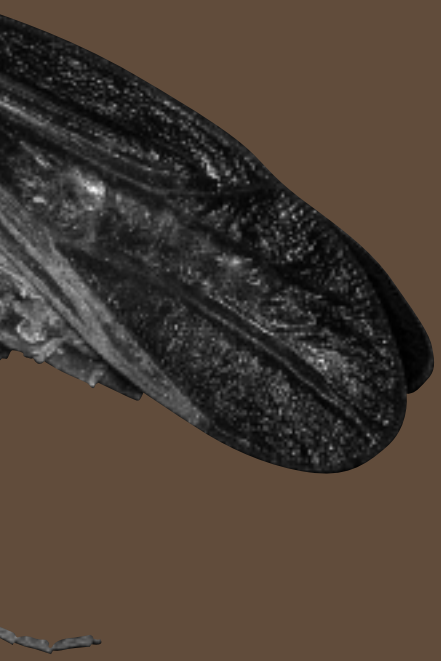
Figs 1 and 6: von Moos Stahl, Emmenbrücke, Switzerland.

Fascinating Amber

Figs 1 and 2 (above):
Amber with inclusion. On the right, Chironomus plumosus.

Figs 3 and 4:
A tick and detail of a scale insect.

Amber, the fossil resin of long-vanished forests has fascinated mankind from times immemorial. The frequent inclusions of plants and animals have made amber not only a material of choice for religious artifacts and works of art, but also an object of scientific interest. The oldest fossil-rich amber we know originates from Lebanon and is roughly 130 million years old. The best known European amber comes from the Baltic and is about 40 to 50 million years old. The inclusions – usually small insects – are often very well preserved and provide an exceptionally detailed impression of what living creatures were like millions of years ago.



The often very small inclusions are usually studied under stereomicroscopes in reflected or oblique light. However, the resolutions achieved in this way are often not sufficient to identify minute morphological structures (e. g. mandibles, genital organs, extremities) required for the systematic classification of insects.

Other microscopic methods can hardly be used for this purpose: transmitted-light examinations are unsuitable due to the thickness and material of the specimens involved, while reflected-light examinations are impaired by reflection, refraction and schlieren in the amber. At high magnifications, the complex 3D structure is almost completely superposed by stray light from non-focal planes.

details

Amber

Scientifically speaking, amber is a *biolith* (bios – life, lithos – stone) and is found in all continents except the ice-covered Antarctic.

Arguably the most famous amber comes from the Baltic, the "mare balticum". Ancient records frequently describe it as "gold of the north", and Nordic sagas speak of "tears of the sea". The most abundant deposits are found near Kaliningrad and on the Samland shore.

The Roman Empire also mentions amber in mythological treatises, describing it as "petrified sun beams" or "tears of the gods". Amber was burnt as incense, its powder was long considered a remedy, and under the name of "eye stone" pieces of amber were used as a cure for eye diseases.

Amber is the petrified resin of primeval trees. In the Baltic region, a species of pine tree from the tertiary period – *pinus succinifera* – is assumed to be the source of amber. The primeval plants and animals trapped in amber are called inclusions. Apart from its individuality and paleogeological significance, the distinctive feature of amber is its vast and fascinating diversity of colors which developed over millions of years of amber formation, depending on the crystallization conditions involved.

The color spectrum ranges from yellow, white, red and green through blue, brown and black to silver and gold, and a single piece of amber may typically display fascinating color variations besides its basic color. The scientific facts look far more sober: amber consists of 67% to 87% carbon, 8.5% to 11% hydrogen and up to 15% oxygen. In addition, it contains small quantities of sulphur, turpentine, derivates and resin acids. The colors of amber range from honey-yellow to nearly transparent and dark brown. Amber dissolves in alcohol and ether, it melts at 300° C and begins to burn.

Fig. 5:
Route of the Amber Road from the Baltic to the Adriatic.

Fig. 6:
Homoptera.

Razor-sharp images

This is where confocal laser scanning microscopy opens up totally new possibilities. A laser beam scans the inclusion point by point and plane by plane, and stray light is effectively suppressed by the confocal pinhole. The instrument detects either the reflected laser light or fluorescence produced in the specimen. The result is a stack of individual high-contrast planes with minimized stray light known as optical sections, permitting 3D reconstruction of the specimen. The images which are reminiscent of those obtained with scanning electron microscopes display a resolution by far surpassing anything seen before. This ensures a significantly higher degree of reliability in systematic classification, especially of insects.

An accidental discovery

The excellent suitability of confocal laser scan microscopy for this highly specialized application was discovered more or less by accident. A private collector contacted Carl Zeiss to inquire about state-of-the-art examination methods for amber, enclosing a few specimens with his letter. The results obtained were so impressive that the collector presented them on his home page in the Internet. The team of *Professor Rust* (now at the University of Bonn) came across these pictures when looking for preservation methods to prevent normal aging in the amber artifacts of the famous Kaliningrad collection which is managed and researched at the University of Göttingen. This was the beginning of a very fruitful cooperation culminating in the exhibition "The Amber Forest by Laser Light" at the Goldfuß Museum of the University of Bonn. This exhibition was part of the "Year of Geo-Sciences" and displayed a selection of outstanding photos plus a host of interesting information about amber and a large number of valuable original pieces.

The wide coverage in regional and national newspapers and in different scientific magazines on TV testifies to the unbroken fascination evoked by amber and the creatures trapped in it millions of years ago. The European Amber Road project – leading from Palanga to Trieste – was recently launched in Austria.

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details

Amber – Tears of the Gods

In the second book of his mythological world history entitled "Metamorphoses" the Roman poet *Publius Ovisius Naso* writes in the chapter "Phaeton" about tears turning into amber.

… quid faciat mater, nisi, quo trahat inpetus illam,
huc eat atque illuc et, dum licet, oscula iungat?
non satis est: truncis avellere corpora temptat
et teneros manibus ramos abrumpit, at inde
sanguineae manant tamquam de vulnere guttae.
'parce, precor, mater', quaecumque est saucia, clamat,
'parce, precor: nostrum laceratur in arbore corpus!
iamque vale' – cortex in verba novissima venit.
inde fluunt lacrimae, stillataque sole rigescunt
de ramis electra novis, quae lucidus amnis
excipit et nuribus mittit gestanda Latinis.

Publius Ovidius Naso,
known as *Ovid*

Ovid was born on March 20, 43 BC in the small provincial town of Sulmo (Sulmona) in central Italy. He was educated in Rome, but soon devoted himself to poetry, renouncing a career in law or as a politician. For reasons uncertain to this day, he was banished by *Emperor Augustus* in 8 AD to Tomi on the Black Sea where he died in 17 or 18 AD, leaving behind him an extensive literary legacy.

Amores (love elegies), Heroides (letters written by mythological heroines to the men who left them), Ars amatoria (an instructive poem on the art of love), Remedia amoris (cures for love), Metamorphoses (a mythological world history centered on transformation), Fasti (the Roman festive calendar), Tristia (an elegiac poem), Epistulae ex Ponto (Tristia continued), Ibis (a diatribe on an unnamed enemy in Rome), Medea (a tragedy), De medicamine faciei feminae (an instructive poem on facial treatment for ladies), Halieutica (an instructive poem on fishing), Phaenomena (a poem on celestial phenomena).

Figs 7 to 9:
Brachycera (detail).
Trichoptera.
Sciara (detail).

Protozoologists on the High Seas

Klaus Hausmann

Hartmut Arndt

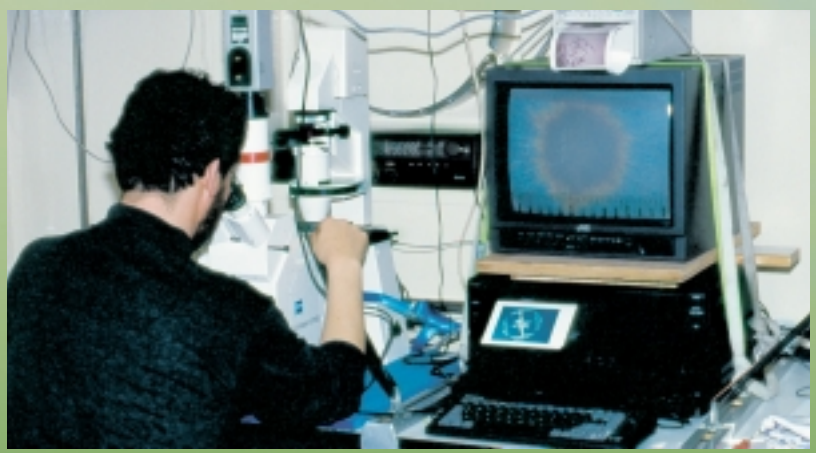
Markus Weitere

More than half of the total surface of the earth is covered by bodies of water more than 2000 meters deep. These deep underwater environments are permanently dark and subject to huge hydrostatic pressure. They are home to bizarre organisms that have adapted to these extreme conditions. Many of the species living in this habitat, the largest on the planet, have yet to be documented. And very little is known about the biology of the species that have been discovered. Our knowledge of the microscopic organisms in particular is extremely limited. Equipped with the Zeiss research microscopes Axiovert® and Axioskop®, three protozoologists from Berlin and Cologne – *Professor Dr. Klaus Hausmann* from the Free University of Berlin along with *Professor Dr. Hartmut Arndt* and *Dr. Markus Weitere* from the University of Cologne – took part in the one-month expedition on the German research ship METEOR, the aim of which was to discover the deep-sea fauna in the Angola Basin. These three protozoologists' analyses are among the first taxonomic studies performed anywhere in the world of flagellates, ciliates and amoebas living at these depths.

Preparation and departure

No sooner had *Dr. Michael Türkay*, the scientific leader of the expedition from the Senckenberg research institute in Frankfurt, stepped on board than he was warning that "everything needs to be tied down!". All instruments, in particular the valuable microscopes and stereomagnifiers, were fastened using belts and ropes to the numerous hooks that had been fitted to the laboratory walls. On deck, the crew lashed down the large containers holding the sampling instruments. July in the Angola Basin means winter, with strong, even stormy winds. The ship will be pitching and rolling and the participants' sense of balance will really be put to the test. In the research area there is a 2-3 meter swell. Hardly any of the expedition participants know what to expect.

The following morning the ship sets sail for the research area, which lies almost 1000 km off the West African coast. The small port of Walvisbaai slowly disappears from view, and with it the large dunes of the Namib Desert, which rise up spectacularly behind the town. The countless seagulls and flamingos that were visible in the coastal waters make way for real deep-sea birds, which only seek out land when breeding. On board everything is being prepared for the sampling procedure. The protozoologists are already studying samples from the coastal waters as a reference for the deep-sea samples. And there is still time to focus their attention on the surface plankton. The radiolarians with their complex siliceous skeletons, which were so impressively depicted by *Ernst Haeckel* (1834–1919) in his Kunstformen der Natur, prove particularly inspiring for both the scientists and the crew. Using polarized light, *Professor Hausmann* displays the filigree skeletons in bright colors on a monitor, which also impresses the



participants who had previously only seen these single-celled organisms during their studies under simple microscopes.

The variety of the abyssal region

After sailing for around two days, they arrive at the first sampling station. With the help of a modern sonar system, large-format maps of the seabed are generated. The precise sampling positions are determined on these maps. Finally, the first box corer, which will be used to recover sediment, is launched overboard on its five-kilometer journey to the bottom of the sea. The entire sampling process takes almost four hours. When the winch is almost reeled in, the scientists, equipped with helmets, life jackets and sampling vessels, gather on deck. The tension is palpable. But so too is the disappointment when an empty box corer surfaces. Another attempt fails and nervousness increases on board. What if the sediment is too hard for the available box corers? Nobody knows what it actually looks like on this part of the seabed. Eagerly the scientists tinker with the sampling instruments; parts are exchanged and the recovery equipment is pushed into the sediment at different speeds. Eventually they find the answer, and the first sediment is brought on board, to the relieved and enthusiastic calls of the scientists.

Now the real work begins. At each station, samples are brought on board around the clock using various tools. The biologists sort their organisms into groups at all times of the day and night. In the protozoological laboratory the microscopes are running at full speed. Unlike most multi-celled organisms, the protozoa have to be counted while they are alive. This is because, with amoebas and flagellates in particular, fixed samples are virtually worthless for the purposes of taxonomic classification, as the typical movements and forms are lost. For the scientists this means counting and documenting as many as possible. Cultures of the single-celled organisms that are found are also created for subsequent molecular-biological analyses. In the meantime scientists enter the protozoological laboratory one after another with different animal groups. There they can make use of the microscopes to analyze important details.

In the microscopy laboratory it is the microscopic deep-sea world that is being studied, but outside in the waves surrounding the METEOR animals of entirely different dimensions can be admired: large whales surface repeatedly in the immediate vicinity of the ship, spraying fountains of water into the air. An albatross circles the METEOR before disappearing into the horizon. And the nets bring up the larger deep-sea organisms: sponges, crabs, fish with light-emitting organs, strange squids and countless other organisms are recovered.

Signs of human civilization can also be found in the haul from what you would assume to be the unspoiled natural environment of the deep sea, the abyssal region (4000–6000 m): first there is a glass bottle, then a brick is revealed, and time and again plastic bags are pulled up from the depths. In particular the scientists recover cinders – large quantities of them – from the old days of steam navigation. These cinders – initially seen as an annoying and unwanted part of the catch – prove, however, to be extremely interesting from a biological point of view. It was on these cinders that the protozoologists found the highest densities of single-celled organisms. This anthropogenic waste has become a new, preferred and popular biotope. Eventually, everyone manages to adapt to the constant movement of the ship. The pitching and rolling is at its peak at the sampling stations when the ship comes to a halt and the stabilizers have to be pulled in. Lateral inclines of up to 29° were measured, which even prompted a dry yet admiring "not bad" from an experienced member of the crew. You get little sleep during these periods, as you are thrown unceremoni-

Fig. 1 (Page 24, bottom left):
Shell of a foraminifer. Microscopic image in polarized light.

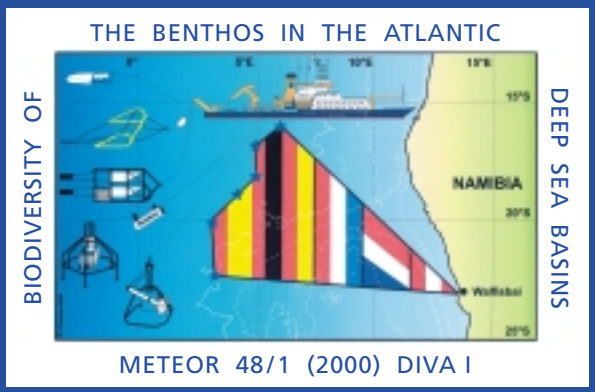
Fig. 2:
Microscopy workstation on board the research ship METEOR. Inverse **Axiovert® 100** microscope with video system.

Fig. 3:
Multicorer, a device for the simultaneous extraction of up to 12 sediment cores, before it was lowered into the abyssal sediment.

Fig. 4:
German research ship F.S. METEOR.

Fig. 5:
Radiolaria.
Microscope image in polarized light.

details



Walvisbaai, Namibia, Africa, 5 July 2000. The German research ship METEOR lies at anchor. As part of the DIVA1 expedition it researched the biodiversity of the deep Atlantic. During the initial four-week expedition of the research program, a 700 km transect of the Angola Basin was studied. This involved retrieving samples from the so-called abyssal benthos at a depth of 5000 m. Using various nets and box corers, groups of organisms of varying sizes, from bacteria through to large fish and crabs, were collected.

An international team of 28 biologists, specialists in various animal groups, were on board the ship. The German participants came from institutes in Hamburg, Frankfurt, Oldenburg, Bochum, Berlin, Cologne and Munich. They included three protozoologists.

ously around your bunk, with one object or another crashing about in the berth. Using a microscope becomes like a balancing act. You have to have one hand ready all the time to hold things down, and looking into the microscope becomes a very strenuous exercise. When analyzing the video recordings back on dry land, in Berlin and Cologne, these memories of heavy seas come flooding back, the constantly changing focus bringing to mind the movement of the water in the culture vessels.

More than 100 unknown species recovered

On the last night of the expedition, the METEOR lies in the roads off Walvisbaai waiting for permission to enter the port. Seals romp about in the ship's spotlight. They approach the ship inquisitively from the mainland and are observed with equal curiosity by the crew. The seals catch fish – something that seems to be a playful and quite incidental activity. The scientists are in excellent spirits. It is roughly estimated that more than 100 species that were previously unknown have been discovered over the course of the past month.

For the protozoologists the results of the expedition were surprising: in contrast to the multi-celled organisms, almost all of the single-celled organisms were already known to them, though admittedly not in a deep-sea environment. These same species are also found in shallow salt and freshwater areas. Some of them had even been found shortly beforehand during the studies by *Professor Arndt's* working group on the natural stone of Cologne Cathedral. The tiny organisms that are repeatedly categorized as primitive species have therefore been shown, in particular, to be outstanding adapters capable of living in virtually all situations and biotopes. In spite of the fact that many of the deep-sea organisms were familiar, however, the protozoologists also discovered two new species in the samples. They had an opportunity to brood over the new scientific names while looking at the seals.

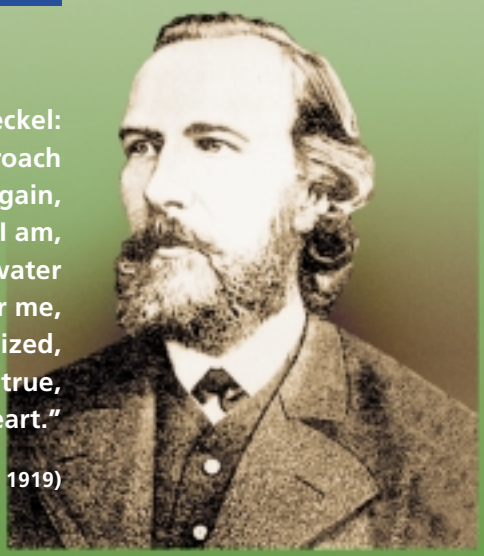
Prof. Dr. Klaus Hausmann, Free University of Berlin, Institute for Biology/Zoology

Prof. Dr. Hartmut Arndt, Dr. Markus Weitere, University of Cologne, Zoological Institute for General Ecology and Limnology

www.biologie.fu-berlin.de/zoologie
www.uni-koeln.de
www.protozoologie.de

Quote from Ernst Haeckel:
"Every time I approach
my dear Mother Earth again,
plunge my whole self into her just as I am,
let the sense of forest and mountains and water
flow directly over me,
I am revitalized,
and a fresh enthusiasm for the true,
the good and the beautiful pervades my heart."

Ernst Haeckel (1834 – 1919)



Eyes for Hollywood

"The Lord of the Rings" in postcard size on a movie screen? This won't make a big splash. To quote "Titanic" director James Cameron: cine lenses are designed for pictures where size matters. When movies are projected, magnifications of up to approx. 1,000 times are no exception.

Cine lenses are key components in determining the quality of a feature film and an investment which must earn money in tough, constant use. Often in conditions to which high-precision units should rather not be subjected: heat, cold, vibrations, shocks, sand, rain, snow, smoke, dust, oil mist…

In addition, cine lenses are usually rental units which must provide reliable service over tens of years without any noticeable downtimes to meet the profitability goals of the rental firms. How, then, are these high-precision units made and what are the requirements they have to meet?

Special conditions of use – special handling

Unlike lenses for still cameras, cine lenses are focused not only before the picture is taken, but also and in particular during shooting. Any play, the so-called "backlash" in the focusing drive would have annoying consequences as would, of course, lateral or rotatory image shift. For this reason, the mechanical systems of cine lenses must be designed and manufactured to provide high precision and a long life.

The "focus puller" must be able to rely fully on the focusing scale. It is his tool for checking image definition. For this reason, good cine lenses come with scales specifically calibrated for their focal lengths. A scale engraved for the standard focal length of 50 mm would not be exact if the effective focal length of the lens used was, for example, 50.18 mm. For this reason, Carl Zeiss provides all of its cine lenses with scales specifically calibrated for their focal lengths.

Color fidelity is also important – not only in a single lens, but throughout the entire line of lenses. Even the smallest deviation can cause extra work during post-production. For this reason, Carl Zeiss computes and produces its cine lens sets in a 'super-color-matched' design, ensuring that no color shift occurs when the focal length is changed. But these are only a few of the special challenges for which Carl Zeiss has developed optimum solutions based on the experience gained in over 150-years.

Since 1907, Carl Zeiss has supplied relatively high-speed lenses of the **Tessar®** type for cinematography. The current Carl Zeiss line for cinematography comprises over 40 different lenses including complex lenses with ultra-high speed and lenses with variable focal lengths.

Manufacture of lens elements

In 1998, Carl Zeiss built the world's most modern lens element manufacturing plant equipped with computer-controlled milling, grinding and polishing machines, MRF asphere technology, high-precision interferometers for quality assurance, ultrasonic cleaning systems for lens surfaces, high-vacuum coating systems for the anti-reflective coating of lens elements, special units developed by the company itself for creating super color matched cine lens sets.

Fig. 1:
ULTRA PRIME lenses for Arri during assembly at Carl Zeiss.
(Photo: Carl Zeiss, Hans-Uwe Furtwängler).

Here, Carl Zeiss manufactures the elements for cine lenses: each surface is treated individually – with the utmost care and with repeated checks of the mechanical and optical precision. The resultant accuracy is similar to that of optical systems used in scientific instruments and therefore is ten times higher than the accuracy provided by elements used in consumer lenses – and a hundred times higher than what is understood by precision in metal processing.

Optical glass

Today, lens manufacturers can choose between 250 different types of glass and crystal materials with different optical properties. Some of them are almost as heavy as iron, others more expensive than gold. Some will survive for thousands of years, others are chemically or thermally relatively instable and will perhaps not even survive a single year without special protection. Many are neutral in color, others, however, have a slight or even marked color tinge. Carl Zeiss uses a specific selection of approx. 110 types of glass for its cine lenses, supplied primarily by the leading manufacturer of optical glass, the SCHOTT Glas company in Mainz, Germany.

Only by cleverly combining different types of glass with lens elements of different shapes will the optical designer succeed in minimizing the aberrations of lenses to such a degree that the image quality reaches a very high level and the requirements for lenses to be free from any color tinge are met.

High-precision mechanical systems, careful assembly and inspection

The mechanical systems of cine lenses also require accuracy in the micrometer range. This is close to the limits of what can be reliably produced with metals in series – actually it is already beyond these limits. The production of high-quality lenses of this type cannot be compared to industrial mass production. Highly skilled and committed optical and mechanical engineers using special tools and devices must exactly align individual components with each other until the complete products attain a level of quality which could never be achieved by direct assembly.

For instance, each single lens is directly adjusted on the Carl Zeiss K-8-MTF tester to provide maximum optical performance.

The actual focal length of each completely aligned lens is measured. On the basis of the data obtained, the lens is then provided with its own specific focusing scale displaying the exact ranges for this lens. This is also maintained, of course, if, for example, the lens ring on the **Ultra Prime** lenses is changed. Thanks to this sophisticated method, Carl Zeiss also achieves high batch production constancy.

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Special measuring devices

"You can't manufacture more precisely than you can measure" – is one of the truisms of manufacturing technology. This means that the measuring technology available must be 5 to 10 times more precise than the targeted manufacturing precision. For this reason, Carl Zeiss has always de-

Fig. 2:
Computer-controlled processing of lens element surfaces in one of the world's most modern lens element production facilities.
(Photo: Harald Frey).

Fig. 3:
ULTRA PRIME lenses must withstand temperatures of −40 °C.

Fig. 4 (in the background):
Cementing of lens elements, the optical cement is hardened using UV light.

Fig. 5:
The front component is inserted in the barrel of the lens, here in an **ULTRA PRIME** 24 mm lens.

Fig. 6:
Trained eyes check the surface quality of high-precision lens elements.

veloped its own high-accuracy measuring devices, thus maintaining its competitive edge. These optical measuring devices are used worldwide not only by quality-conscious optics manufacturers, but also by governmental and private standards and test institutes, metrology labs used by test journals, and demanding cine rental firms.

Stringent prototype testing

As a manufacturer of high-performance optics for extreme requirements, Carl Zeiss has its own notion of what "adverse conditions of use" are: comprehensively equipped test laboratories allow the simulation of extreme heat, oppressive sultriness, arctic cold, dripping humidity, shaking, vibrations, fall on concrete, impact, shock, cyclical changes in temperature and humidity, supersonic low-altitude flying, rocket launches, high-speed cross-country drives with tanks, salt water spray, truck transport on gravel roads etc. – and even the pressure and temperature extremes that exist in space. Each prototype lens is subjected to a well-considered mixture of these test conditions and then analyzed to find possible ways of improving the prototype and to incorporate any improvements before batch production is started. The current **Ultra Prime** lenses also owe their low servicing requirement to this stringent prototype testing.

ARRI and Carl Zeiss

Since 1937, Carl Zeiss has supplied high-speed cine lenses to Arnold & Richter. A wide range of cine lenses is now being developed exclusively for and together with ARRI and produced for this company. Carl Zeiss and ARRI are constantly in touch to discuss new optical product ideas and to check them for their economic and technical feasibility. The modern **Ultra Prime** set with its now 15 different focal lengths and the set of **Ultra Prime** LDS lenses for the new ARRIcam derived from it are the most impressive results of this cooperation to date. But this is a continuing process: new ideas are already under discussion… Let's hope that they will be as successful as the known lines of lenses which have already been honored with awards.

Recognized by professionals

The **Ultra Prime** lenses have now become the most popular high-performance lenses in the cine industry: almost 500 sets are now available worldwide. Major films have been shot using these lenses, including spectacular productions such as "The Lord of the Rings".

But predecessor lenses were also successful: the large number of the ultra-high-speed Carl Zeiss lenses **T 1.3** and the **Variable Prime** lenses which are lenses with variable focal lengths but which provide the speed and image quality of lenses with fixed focal lengths. The Academy of Motion Picture Arts and Sciences honored ARRI and Carl Zeiss with a "Scientific and Engineering Award" for both lens lines.

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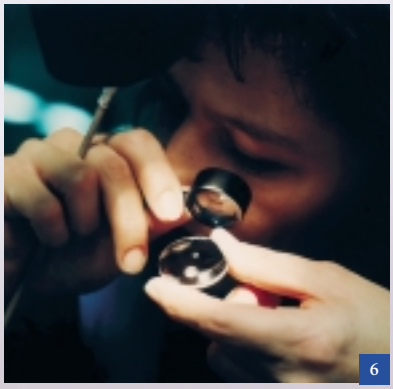
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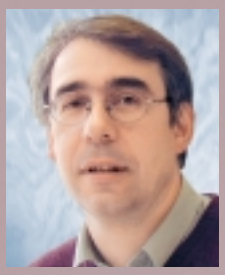
The "Eagle Eye of Your Camera" in the Ballo



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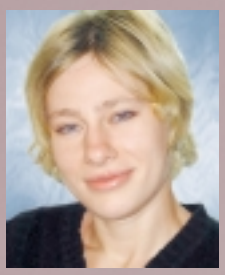


Katarina Horn

From *Icarus* and *Daedalus* to the *Tailor* of *Ulm*, the dream of lifting off into the ether like a bird has haunted mankind through the ages, a dream which, until 1783, was doomed to failure by the law of gravity, all attempts ending in a painful crash to earth or at best a splash. It was not until the invention of the hot air balloon that the age-old dream was fulfilled. On September 19th 1783, watched by King Louis XVI of France and 130,000 spectators at Versailles, the first hot air balloon to carry live occupants, the "Martial", took to the skies. Its passenger complement: a cockerel, a sheep and a goose. The next attempt came a few weeks later when aeronauts *Pilâtre de Rozier* and the *Marquis d'Arlandes* became the first human beings to fly in a balloon, floating for 25 minutes above the Seine.

When the first manned gas balloon took off some time later, two types of flying machine had made their mark. Soon the art of flight had spread beyond the borders of France and claimed its first victims. Before long, height and distance records were tumbling one after the other, and ever new uses were found for the popular craft. They were used as reconnaissance craft for military purposes and from 1804 for various types of scientific research including meteorological investigation.

In 1858 *Gaspar Félix Tournachon*, known as *Nadar*, took the first photographs from a balloon, thus combining two technical innovations, which reach their apogée in today's high-resolution satellite photos.

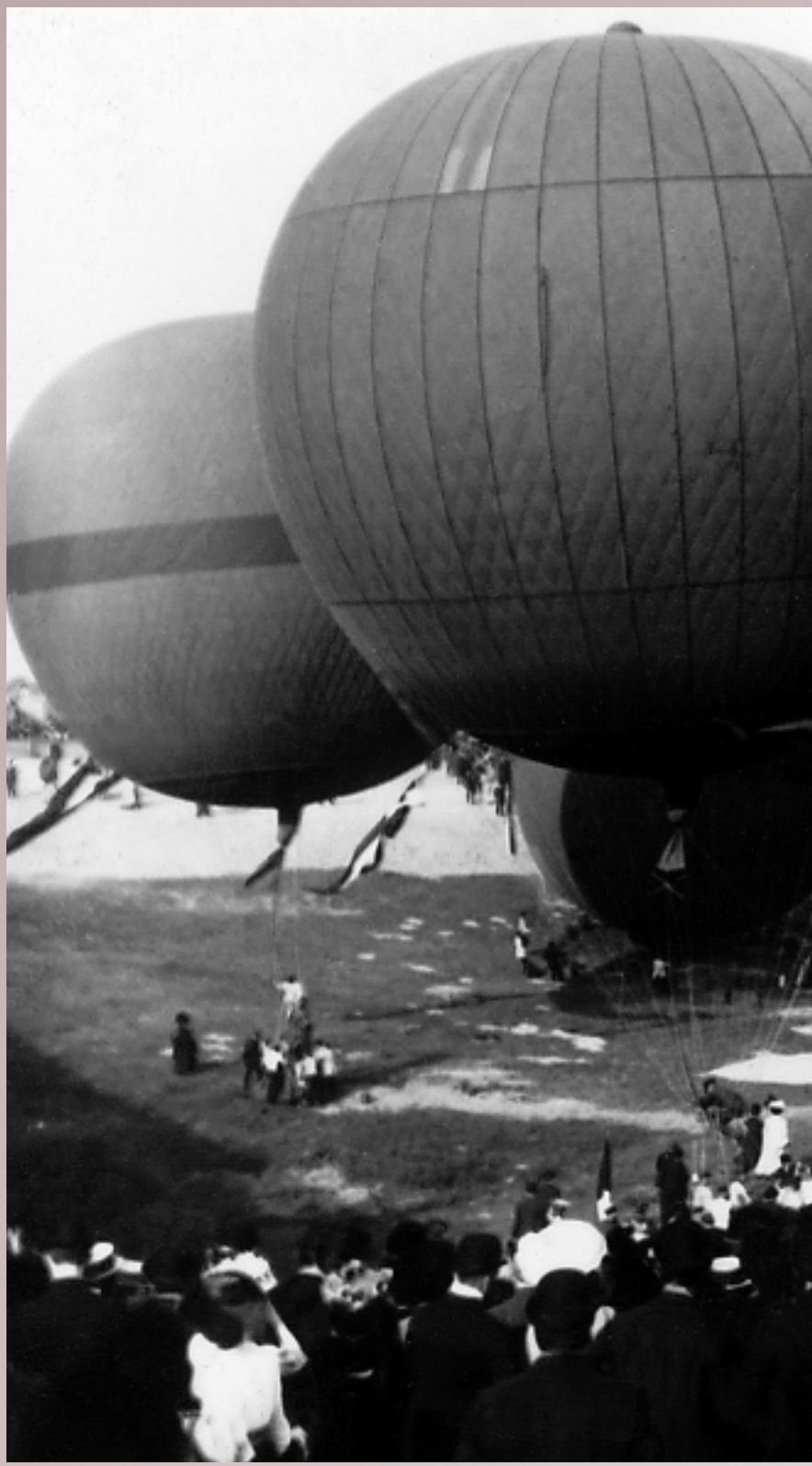
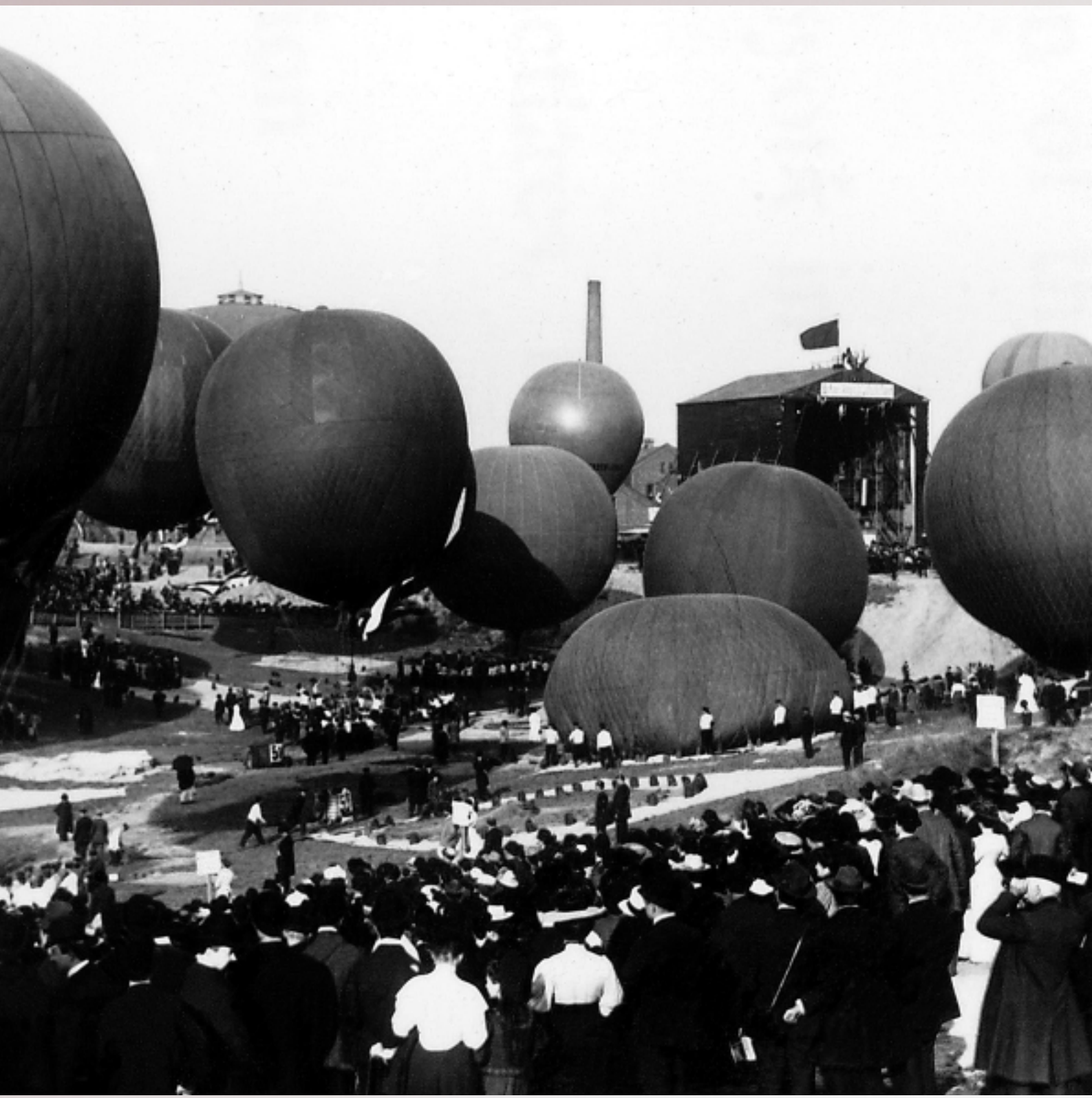


Fig. 1:
Balloons on the Berlin airstrip.

on Age



Physicist, photographer and balloonist

Carl Zeiss has been manufacturing cameras and plotters for scientific photogrammetry ever since 1901. The early products are closely associated with the name *Carl Pulfrich* (1858–1927). But Carl Zeiss staff were not just pioneers in instrument design; they made important advances in use of the equipment as well. One outstanding practitioner was *Ernst Wandersleb* (1879–1963), who started work in the camera lens department of the company in 1901 as assistant to *Paul Rudolph* (1858–1935). An enthusiastic balloonist, on February 20th 1905 *Wandersleb* became an "ordinary member" of the German aviation association. Four months later he embarked on a series of flights throughout Germany and as far as Austria and Switzerland, first in the "Tschudi", followed by the "Thüringen", the "Altenburg", the "Gross", the "Erfurt" and the "Clouth", taking numerous aerial photographs, most of them with the famous **Tessar®** lens developed by *Rudolph* exactly 100 years ago in 1902. In 1911 *Wandersleb* succeeded *Paul Rudolph* as head of the Carl Zeiss camera lens department, and took a leading role in its activities until his retirement in 1957. During these years he continued to develop the **Tessar®**, writing 27 learned papers on the subject and registering 19 patents and prototypes, which stand as a monument to his professional contribution to photographic optics.

Today the aerial photos *Wandersleb* took on his trips between 1905 and 1913 form a unique resource for the history of scientific photogrammetry, photographic optics and, indeed, geography, which relies heavily on aerial photography as both a reference for historians and a planning tool for applied research. By far the

Fig. 2:
Burg Saaleck at Camburg
Dec. 11, 1910.

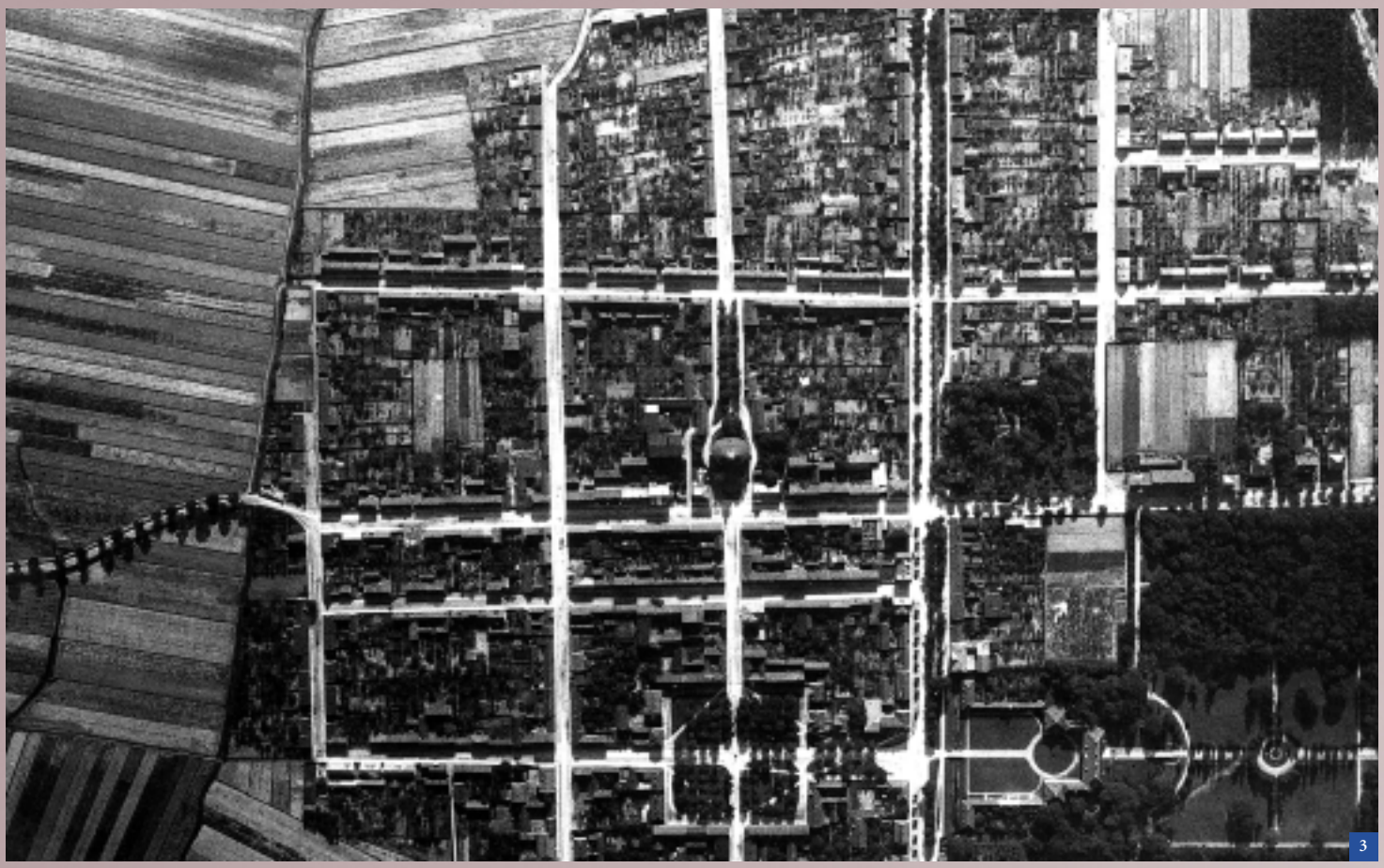


Fig. 3:
The Anhalt town of Oranienbaum.

greater part of his work is now held in the pictorial archive of the Institute of Regional Geography in Leipzig, to which it was donated at *Wandersleb's* request in the early 1960s.

At the start of the 20th century balloon lift-offs and landings were still highly popular events, attracting large crowds of fascinated spectators. Starting points were not easy to find and depended on the proximity of fixed gas supplies. As *Wandersleb* himself reported proudly, he started his balloon trips "not only in Jena, but in 15 other towns, most of them having highly unsuitable gas works and totally inexperienced assistants, yet I never had a serious accident either taking off or landing." At the same time he was training new balloonists, and reports of his trips appeared weekly in the local press in Thuringia.

Aerial photographs

Most of his flights were confined to central Germany – Thuringia and Saxony – but occasionally he got as far as the Baltic See, the Rheinland or the Alps. The "Thüringen" took him as far afield as Pommerania, Silesia, Bohemia, Hesse and the Eifel. His photographs include both vertical and oblique perspectives taken from different heights between 100 m and over 2,000 m. All taken with the **Tessar® f/6.3** lens (15 cm focal length) developed by Carl Zeiss, the quality of some of them is strikingly good. Fig. 3 shows a vertical shot of the Anhalt town of Oranienbaum from a height of 1,600 m. The regular lines of the planned baroque town center are clearly evident. Fig. 7 is an oblique shot from 100 m up of Glaubitz near Riesa, a substantial little peasant settlement sitting among its fields; in the foreground the center of the village with its church dating to 1589 and the former Schloss precincts dating to the first half of the 18th century.

Wandersleb's shots must be the earliest aerial photos ever taken of many of these settlements. Depicting towns and villages, tilled fields and uncultivated land as they were 100 years ago, they are important sources for genetic agricultural geography. The original lines of the mature agricultural landscape are still visible, the original field markings and their uses

Fig. 4:
Filling the balloon, the "Gross", in Jena on Aug. 25, 1908.

Fig. 5:
Lifting off in Frankfurt a. M. on Sept. 25, 1909.

have not yet been obscured by land reform and clearing; many of the villages suggest their still purely agricultural way of life, while urban layouts are still unmarked by the ravages of the Second World War and the subsequent changes in town planning. Oberhof in the Thüringer Wald (Fig. 10), already a health resort noted for its fresh air and attracting 10,000 visitors a year, still gives little indication of its later spectacular development as a tourist resort and winter sports center. Some of the pictures create a positively eerie impression: the distinctive towers of the ruins of Saaleck castle at Camburg emerge from the wreaths of mist in Saaletal like a fairytale castle (Fig. 2).

The photographs in the Leipzig archives

Ernst Wandersleb's photographs are held in the Leipzig archives as individual prints or in albums and most of them are carefully captioned. Especially valuable are those he painstakingly documented, including in the log with the photo itself the exact date and location of the subject and additional photographic, meteorological and geographical data. He photographed the Hamlet Sprakensehl in the Lüneburger Heide (Fig. 8) on March 7th 1909 at 4.06 p.m. from a height of 800 m.

One flight in the balloon "Thüringen" took him from Jena to Roten-

Fig. 6:
Minimum Palmos focal plane shutter camera for 9 x 12 cm plates and film with 15 cm **Tessar®** f/6.3 and shutter speed to 1/1,000 sec., 1902.

Fig. 7:
Oblique shot of the village of Glaubitz near Riesa from a height of 100 m.

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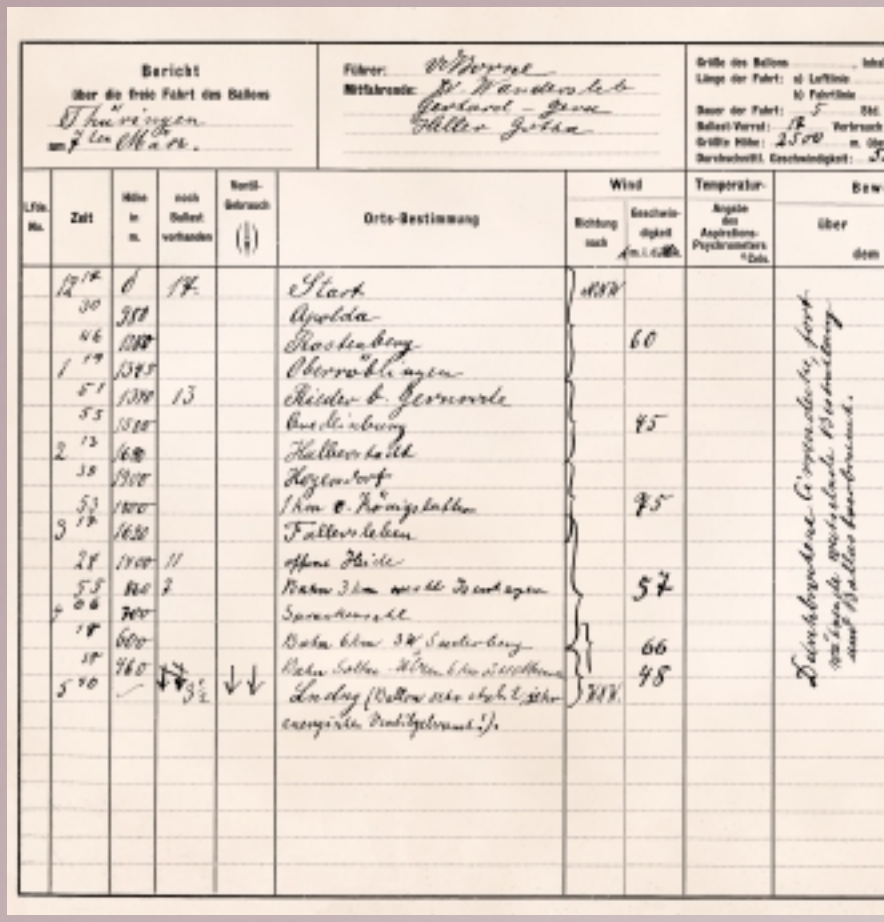


Fig. 8:
Page from the log of the balloon "Thüringen" showing hamlet Sprakensehl in the Lüneburger Heide.

Fig. 9:
Page dated March 7, 1909 from the log of the balloon "Thüringen".

Fig. 11:
Route map from Jena to Rotenburg/Wümme.

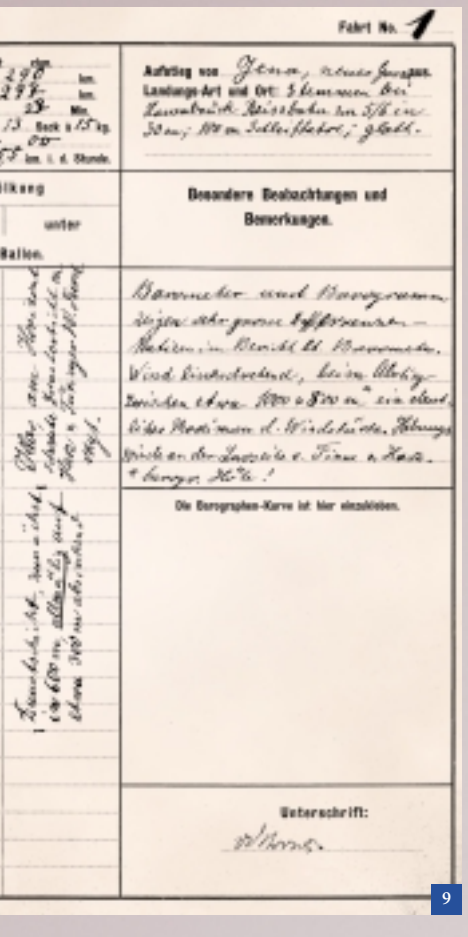
burg/Wümme, as his route map shows us (Fig. 11). The map is included in the logbook shown, which gives more information on the flight and how the photograph was taken. Photo, data sheet and the entry in the logbook all provide a unique historical and geographical record testifying to *Wandersleb's* lively scientific curiosity.

As well as the oblique and vertical aerial photos, the collection includes numerous shots of cloud formations or other tied balloons he came across. He was even able to log and capture on film the occasional sightings of motorized aircraft, still a rarity in those days.

Along with his own work *Wandersleb* collected aerial photographs made by other German balloonists such as *Baron Konrad von Bassus*, who belonged to the Munich aviation association or *Lieutenant Wilckes* from Friedrichshagen. Like *Wandersleb*, these two wrote reports on their various flight routes accompanied by photographs, and as well as using the Zeiss **Tessar® f/10, f/20, f/6.5** and **f/4.5** lenses of various focal lengths, also tested the **Apotessar®** or used systems produced by competitors, such as the "Aplanat" (1909), the "Extra-Rapid Aplanat" (1911, 1912), the "Dopp. Anast. Goerz" (1909) and the "Ernemann" (1911).

For the photographic historian, flight historian and the historical geographer alike, *Ernst Wandersleb's* collection is a priceless treasure, which has languished for too long in obscurity. Apart from a few of the items that were displayed at exhibitions in Berlin in 1989 and Leipzig in 1995, the collection has never been shown to the public before. The Institute of Regional Geography has the technical means to digitize the photographs and make them available on the Internet as soon as the funds are available.

Fig. 10:
Oberhof on March 20, 1910 from 800 m.



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Heinz Peter Brogiato, Katarina Horn
Institute of Regional Geography
www.ifl-leipzig.de

11

details

Dr. Ernst Wandersleb (1879–1963)

In 1901 *Ernst Abbe* took the physicist *Dr. Ernst Wandersleb* into the camera lens department of the Zeiss factory in Jena. To start with he was employed as an assistant to *Paul Rudolph*, working mainly on the computing of new camera lenses. *Wandersleb* realized early on that the speed of the **Tessar®** lens could be increased. October 1904 saw final calculations for the **Tessar® f/4.5** completed and the lens that became known as the "eagle eye of the camera" was ready for production. At the age of 32 *Wandersleb* succeeded *Paul Rudolph*, inventor of the **Tessar®** lens, in his post at Zeiss.

The Zeiss plant photographed using a Minimum-Palmos camera in 1910. 150 mm **Tessar® f/4.5** lens.

Apart from physics, *Wandersleb* was interested in astronomy and zoology. He was also a keen mountaineer, conquering Mont Blanc (4,807m) in 1911. Jena remembers him, too, as a great supporter of the city's musical life. Together with *Fritz Stein* he resurrected the Naumann Academic Choir, rechristened the Philharmonic Choir in 1918. In 1908 he founded the Thuringia aviation association with professors from Jena University and Zeiss colleagues. On his more than 40 balloon journeys up to 1912 *Wandersleb* gained the valuable experience that he could apply at Zeiss in the design of instruments for aerial reconnaissance.

The Environment Was One of the W

Fig. 1:
The yacht "illbruck".
At the start of the second leg from Cape Town to Sidney.

Oceans cover roughly seventy percent of the earth's surface. Being far less accessible than the mainland, their exploration presents a particular challenge. In addition, oceanography requires the use of dedicated, multidisciplinary working methods. Marine physics as a sector of oceanography, for example, includes biological and chemical methods scarcely found to the same extent in other areas of physics.

The world's toughest yacht race

The Volvo Ocean Race, previously called the Whitbread Round the World Race and held for the first time back in 1973, is generally considered to be the world's toughest offshore yacht race.

At the end of this nine-leg challenge, the overall victory in 2002 went to the German boat "illbruck" on June 9. At the same time, this year's race was also an endurance test for 24 MMS-1 spectrometers from Carl Zeiss. Each of the eight yachts entering the race had three of these optical sensors on board. As part of the environmental project Volvo Ocean Adventure launched together with the race, the spectrometers were used for measuring water quality. The data obtained was compared with concurrent satellite measurements and evaluated. The results are made available by Volvo in the Internet for research and training purposes.

The spectrometers had to cope with truly rough conditions: hard shocks, high waves, and extreme

Fig. 2:
The yacht "illbruck". On the second leg from Cape Town to Sidney.

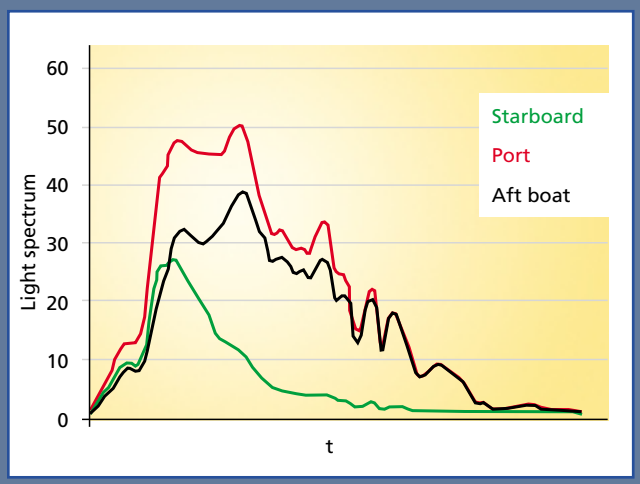


Fig. 3:
Measuring device with MMS-1 spectrometers from Carl Zeiss at the boat's stern.

Fig. 4:
Light spectrum recorded over time.

inners

temperature variations. Nevertheless, they had to measure with an outstanding accuracy of within a tenth of a nanometer. Their seaworthy enclosure was provided by Trios Mess- und Datentechnik GmbH in Oldenburg, Germany.

Detecting environmental damage through absorption and reflection

Light is absorbed and scattered by the substances dissolved or suspended in water. In addition, many organic substances display fluorescent phenomena when exposed to ultraviolet or visible radiation. The knowledge of these properties can be utilized for the optical determination of substances in the ocean. Algae and suspended matter discharged by rivers in the coastal regions can be detected with a high degree of sensitivity.

The relevant exploration methods and the Zeiss spectrometers are not only used in oceanography, but also in environmental monitoring, permitting the detection of dissolved organic substances and of pollution by oil and chemicals.

At the Carl von Ossietzky University in Oldenburg, Germany, the team of *Rainer Reuter* which closely cooperates with Trios Mess- und Datentechnik GmbH focuses on the development and use of optical methods for the exploration of the oceans.

Volvo Ocean Adventure

The environmental project Volvo Ocean Adventure sponsored by the Swedish vehicle manufacturer Volvo involved the use of spectrometers, and the data obtained is now generally available. The yachting professionals had committed themselves to take the spectrometers on their journey, although the crews had gone out of their way to save every gram of weight in the equipment on board: only one tube of toothpaste was allowed for a crew of 12, clothes were used instead of pillows, and the toilet had no walls.

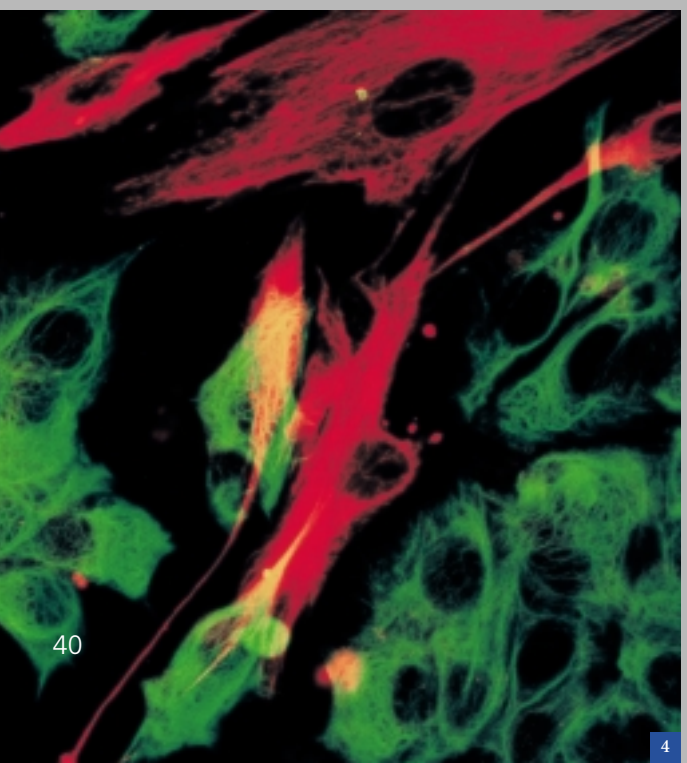
www.zeiss.de/spektral
www.volvooceanrace.org
www.uni-oldenburg.de
www.trios.de

L'ORÉAL/UNESCO Award for Mary Osborn

Fig. 1:
Mary Osborn from Göttingen at the **Axiophot®** microscope from Carl Zeiss.

The L'ORÉAL/UNESCO Awards were presented in March 2002 at the UNESCO headquarters in Paris by *Lindsay Owen-Jones*, Chairman and CEO of L'Oréal, and *Koichiro Matsuura*, Director General of UNESCO. Five women scientists, one from each continent, were honored with the L'ORÉAL "For Women in Science" Award with a prize of US$ 20,000 for each laureate in recognition of their major contribution to the advancement of science.

The jury under the presidency of *Christian de Duve* – 1974 Nobel Prize for Medicine – is composed of eminent members of the international scientific community. *Christian de Duve* highlighted the diversity of the 2002 awards: "We have been given a magnificent panorama of science in the service of humanity: from fundamental research to clinical applications, and the development of fundamental technologies."



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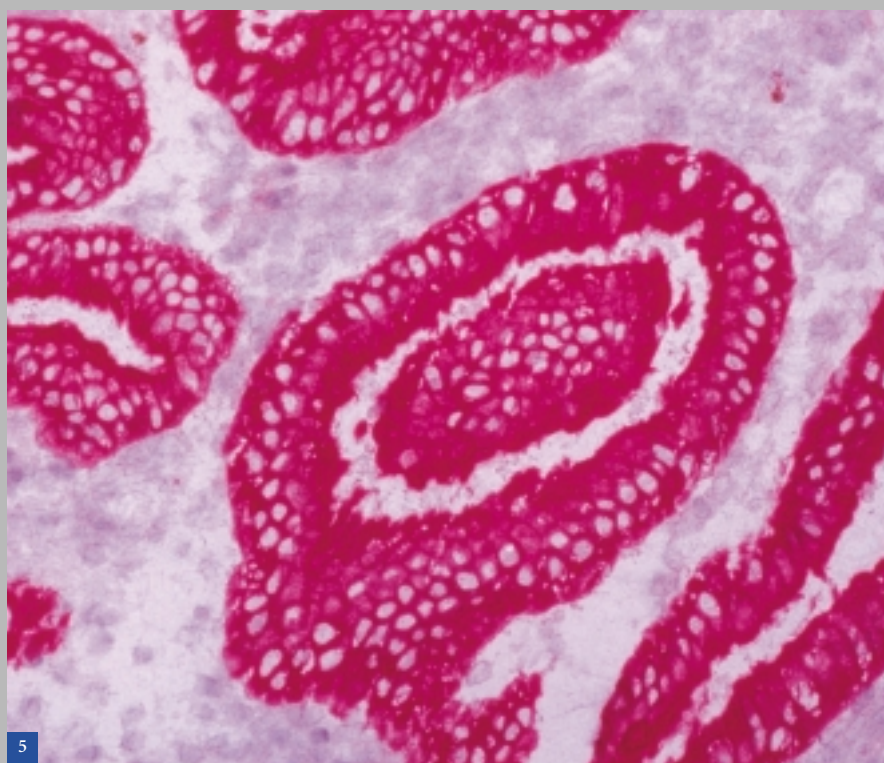

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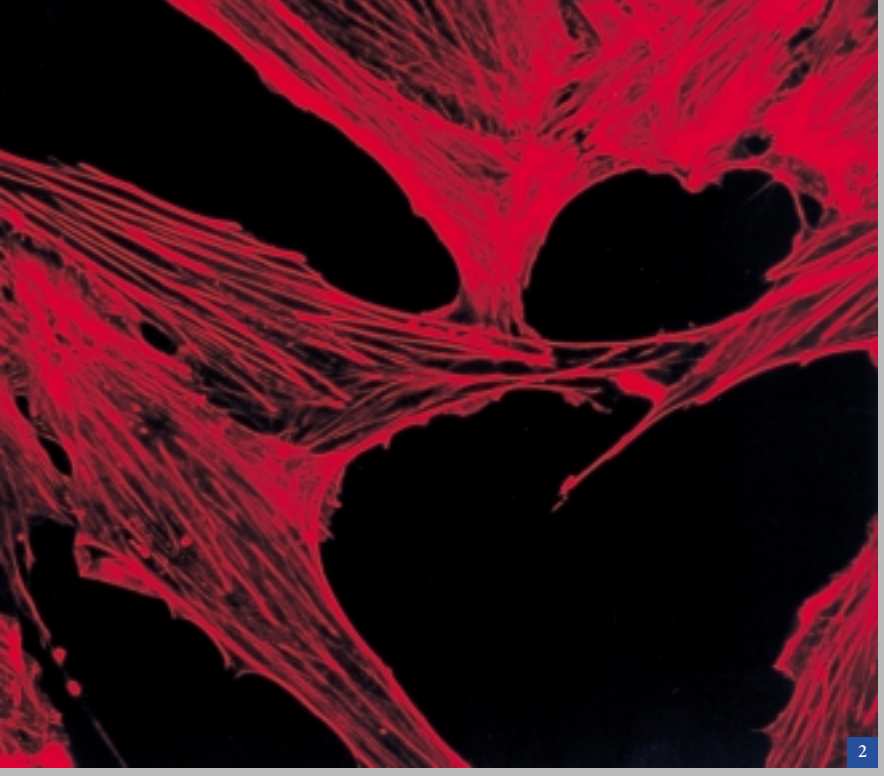
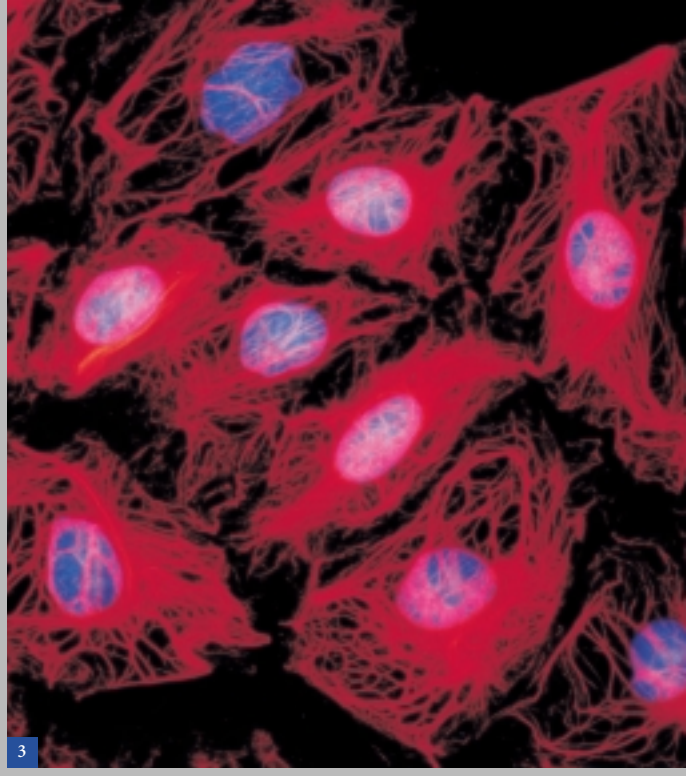




Among the five laureates was *Mary Osborn* from Göttingen. Her development of an immunofluorescence microscopy technique permitting the localization of proteins was seen by the jury as a pioneering achievement and was decisive for conferring the award on her. Researchers all over the world are now using this microscopy method for the observation of cell structure.

Mary Osborn has been a scientist with the Max Planck Institute of Biophysical Chemistry in Göttingen since 1975. Her research activities in molecular biology are focused on the proteins and structures of the cell nucleus and the use of antibodies in cancer diagnosis. The institute has pioneered the use of antibodies in immunofluorescence microscopy. In particular, the distribution and function of two ubiquitous filament systems – microfilaments and microtubules – were investigated. The major proteins in these systems are actin and tubulin. This knowledge has now permitted intermediate filament proteins to be used as differential markers in tumor diagnosis.

Further scientists working at the Max Planck Institute of Biophysical Chemistry (Karl Friedrich Bonhöffer Institute) in Göttingen include *Prof. Peter Gruss* (President of the Max Planck Society), *Prof. Thomas Jovin, Prof. Erwin Neher, Prof. Klaus Weber and Dr. Stefan Hell*.

Professor Mary Osborn, Max Planck Institute of Biophysical Chemistry, Göttingen, *mosborn@gwdg.de*

Fig. 2:
A cytoplasmatic filament system in cultured cells: actin microfilaments.

Fig. 3:
Intermediate filaments: keratin (red), DNA (blue).

Fig. 4:
Intermediate filaments typical of different cells: keratin (green) in epithel cells, vimentin (red) in fibroblasts.

Fig. 5:
Intermediate filaments as tumor markers typical of different cells: histological section of a carcinoma, keratin-positive tumor cells (red).

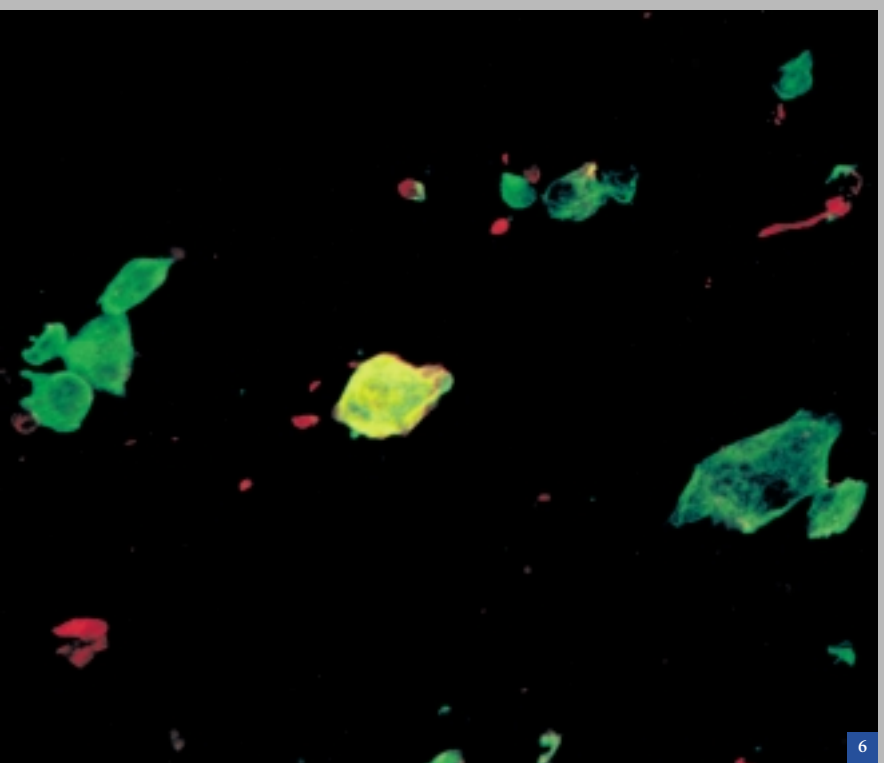


Fig. 6:
Cytological specimen of a mammary carcinoma: keratin-positive tumor cells (green), other cells are vimentin-positive (red).

Microscope from Carl Zeiss Receives R&D Award

Fig. 1:
Scan module of the **LSM 510 META** at the **Axioplan® 2** imaging **MOT**.
1 Light guide
2 Motorized collimators
3 Beam combiner
4 Main dichroic beam splitter
5 Scanning mirrors
6 Scanning lens
7 Secondary dichroic beam splitters
9 Pinhole
8 Emission filters
10 Photomultiplier
11 META detector
12 Neutral density filters
13 Monitor diode
14 Fiber out

In 2002, the LSM 510 META Laser Scanning Microscope from Carl Zeiss was one of the winners of the renowned R&D 100 Awards granted every year by the R&D Magazine. This US magazine with a monthly circulation of 90,000 copies awards the "Oscar of inventions" to the 100 most important technical products launched worldwide.

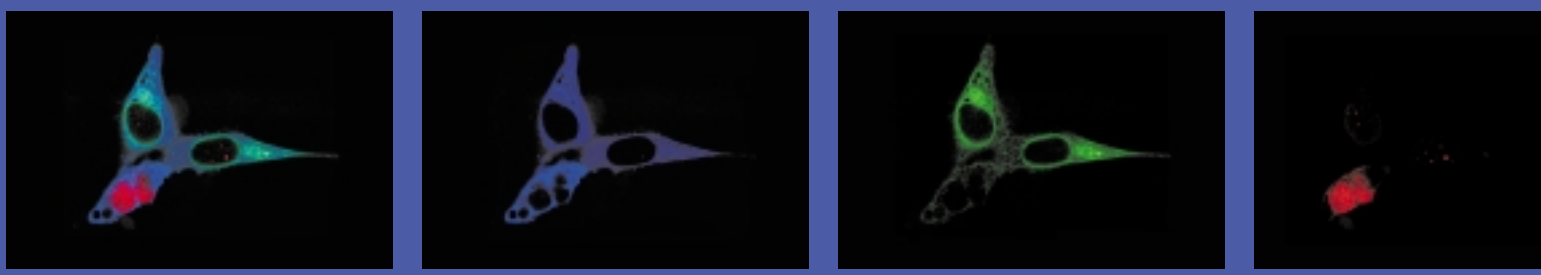


Fig. 2:
Cultured cells: expression of ECFP RanGAP1 (blue), EGFP emerin (green) and EYFP-SUMO1 fusion proteins (red). Emission Fingerprinting displays the different subcellular distribution of proteins in cytoplasm, endoplasmatic reticulum / core membrane and core.
Prof. Y. Hiraoka, KARC, Kobe, Japan

Thanks to a new confocal detection technique in fluorescence microscopy, the **LSM 510 META** – developed by Carl Zeiss and the California Institute of Technology, Pasadena, USA – opens up experimental possibilities which seemed totally unattainable in the past. The **LSM 510 META** has been designed for applications in almost all biomedical research disciplines, from cell biology to the neurosciences and cytogenetics. In all, this is already the 10th R&D 100 Award that Carl Zeiss has received.

The centerpiece of the system is a multichannel detector which not only records brightness distributions in the examined specimen, but also the spectral composition of fluorescence light in each of the scanned object spots. This technique now permits the simultaneous localization of considerably more fluorescence dyes than ever before. Dye combinations not usable in the past can now be used for specimen marking. In particular, the **LSM 510 META** allows strongly overlapping fluorescence emission spectra, such as those of the fluorescent proteins CFP, GFP and YFP, to be precisely and efficiently sorted into separate image channels by means of digital deconvolution algorithms.

www.zeiss.de/lsm
www.rdmag.com

Ernst Abbe Lecture 2002

Professor Stephen Fuller, from the Division of Structural Biology of the Wellcome Trust Centre for Human Genetics at the University of Oxford, has been awarded the Ernst Abbe Lecture. This honor was presented to him on the occasion of the 15th International Congress for Electron Microscopy, held from 1 to 6 September 2002 in Durban, South Africa. More than 300 people attended his lecture entitled "HIV electron microscopy: in search of regularities in a complex virus".

Stephen Fuller, who had already received the Ruska Prize of European electron microscopy companies in Brünn in 2000, originates from Wilmington in the State of Delaware, USA. He is a physicist and chemist and has been working at the University of Oxford since February 2000. Previously he spent almost 20 years as a scientist and group leader at the European Molecular Biology Laboratory in Heidelberg. This year's Ernst Abbe Lecture was awarded to him for his extensive and fundamental electron-microscopy work on viruses and virus structures.

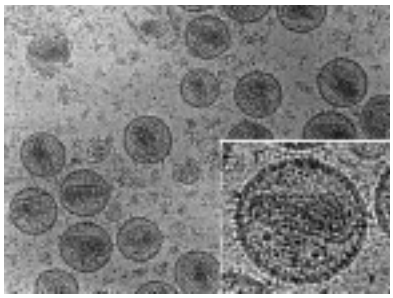


Fig. 1:
Image of mature viruses from the lecture on HIV electron microscopy.

Fig. 2:
From left to right: *Stephen Fuller*, *Aaron Klug* (MRC Laboratory for Molecular Biology, Cambridge, United Kingdom, Nobel Prize Winner 1982), *Heinz Gundlach* (Carl Zeiss).

[*www.zeiss.de*]

Award for Screening Technology

Dr. Klaus Mlejnek, Vice President & General Manager of the Molecular Medicine Division of Carl Zeiss, received the 2002 SBS Accomplishment Award for his pioneering contribution to the development of the **plate::explorer®** Ultra High Throughput Screening (UHTS) system for drug discovery in pharmaceutical research. Every year, the Society for Biomolecular Screening (SBS) honors people who have helped advance the area of drug discovery.

Dr. Thomas D.Y. Chung, President of SBS, explained why *Dr. Mlejnek* received the award: "Your participation in the development of the innovative modular Zeiss systems for specimen screening in all the standard microtiter plate formats with ultrahigh throughput is honored as a major contribution in the area of drug development".

The Society for Biomolecular Screening was founded in 1994 as a forum for education and information exchange amongst professionals within Drug Discovery and related disciplines. The Society offers its more than 2000 members various publications, conferences and learning programs. The SBS Award honors outstanding technical achievements in biomolecular screening. The UHTS system developed by Carl Zeiss permits several 100,000 specimens to be examined every day for their suitability as potential drug. The centerpiece of the system is the **plate::vision®** Multimode Reader permitting the fully automatic measurement of microtiter plates with optimum data quality in an extremely short time.

[*www.zeiss.de/mm*
www.sbsonline.org/awards-grants/02awardees.html]

Photo:
The SBS Accomplishment Award was presented to *Dr. Klaus Mlejnek* during the 8th Annual Conference and Exhibtion of the Society for Biomolecular Screening in The Hague in the Netherlands on September 26, 2002. This conference is the major international event in the area of drug screening, with more than 2100 attendees this year.

Do You Know

Hugershoff Cove

Zeiss Needle

Wild Spur

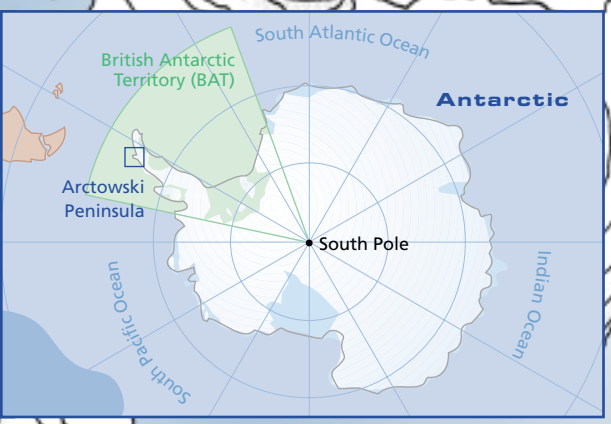
Pulfrich Peak

Brewster Island

Arctowski Peninsula

Porro Bluff

Rudolph Glacier



The place that bears this name is not exactly the hub of the universe. But for geoscientific research the Arctowski Peninsula in the northern Antarctic is nevertheless an area with a future. Recently it has also started to attract tourists in search of a special thrill! But how did the names of half a dozen pioneers of optical instrument development become associated with parts of this inhospitable region?

The principle of paying tribute to the exceptional contributions of explorers, captains, ship owners and adventurers by naming places after them was started by *James Cook* in around 1775. In true imperial tradition, this practise was retained over the centuries and continued up to the middle of the 20th century in the British Antarctic Territory (BAT) by the responsible body, the Antarctic Placename Committee (APC). From this point onwards, new ideas were needed.

Innovation 12, Carl Zeiss, 2002

Where the "Zeiss Needle" is?

Between 1955 and 1957 the Falkland Islands and Dependencies Aerial Survey Expedition (FIDASE) systematically charted 86,000 square kilometers of the peninsula for the first time. When these mountainous, fjord-like, fissured spits of land were being mapped a whole host of new placenames were needed. The use of names of prominent personalities was retained, but a new system was put in place to prevent duplication and to bundle the names of pioneers from certain fields of achievement within certain territories. As a result, 45 groups of names are now used to designate the geographic features in the British Antarctic Territory – names that symbolize particular progress in aeronautics, navigation, oceanography and cold climate physiology, but also in the fields of photography and photogrammetry.

On current maps we therefore find, on the furthest outlet of the peninsula, in addition to the "Zeiss Needle", names such as *"Hugershoff Cove"*, *"Wild Spur"*, *"Pulfrich Peak"*, *"Rudolph Glacier"*, *"Porro Bluff"* and *"Brewster Island"*. In February 2000 the slopes of the *"Zeiss* Needle" were tackled for the first time by a group of skiers and snowboarders led by Rick Armstrong. Whether the new generation of Antarctic explorers, the ever increasing numbers of cruise tourists, the climbers, the divers and the winter sports enthusiasts, who are arriving on the continent are aware of who and what lies behind the names that describe the striking features of this fascinating landscape is another matter.

www.zeiss.de
www.antarctica.ac.uk
www.mountainzone.com
www.air-and-space.com
www.falklands.gov.fk/pb/bat
www.crownagents.com

The people to whom the placenames refer

Carl Zeiss, founder of the optical works of the same name in Jena. ***Carl Pulfrich*** was manager of the optical measuring instruments department in Jena. With the development of the stereocomparator he introduced the stereoscopic measuring principle into photogrammetry. This laid the foundation for photogrammetric instrument production at Carl Zeiss. ***Paul Rudolph*** was manager of the photo department in Jena and creator of the "Tessar" lens, which was patented 100 years ago this year. ***Reinhard Hugershoff*** was an employee of the company Aerotopograph in Dresden, which later became Zeiss-Aerotopograph in Jena. ***Heinrich Wild***, a developer of land surveying instruments, worked at Carl Zeiss in Jena from 1908 to 1919. In 1921 he founded the company Wild, Workshops for Precision Mechanics and Optics in Heerbrugg. ***Ignazio Porro***, an Italian artillery officer, constructed the first prism reversal system for telescopes in 1854. ***David Brewster***, a Scottish physicist, formulated the law on polarization that bears his name in 1811. He invented and patented the kaleidoscope.

Fig. 1 (background):
Andvord Bay, Antarctic Peninsula, Antarctic, January 2001.
Photo: *Brian Lockett*

Fig. 2:
Stamp from the series commemorating the history of land surveying.

Fig. 3:
Ski and snowboard excursion, Wiencke Island.
Photo: *Kristoffer Erickson*

Fig. 4:
Zeiss Needle.
Photo: *Kristoffer Erickson*

Dipping into Real and Virtual Worlds

At the World Summit on Sustainable Development in Johannesburg held from August 26 to September 4, 2002, the automobile manufacturer BMW presented itself using projection technology that is unique in the world. The Laser AllDome projection system from Carl Zeiss was installed in the BMW Group Earth Lounge and projected oversize color video images in unprecedented quality.

In a semitransparent 24-m dome floating on air and symbolizing the earth, the BMW Group held lectures, seminars and other events on environment-related topics for the summit participants, the general public and the media. The dome boasted two world premieres: all-dome projection was presented to the international public as an all-time first, and the coverage of a 700 m^2 surface made it the world's largest projection to date. Despite indoors illumination and light outside, the images had to be brilliant and sharp.

This enhanced the overall attractiveness of the BMW presentation. Ms. N. Stempinski, responsible for marketing and communication at BMW CleanEnergy, described the effect of laser all-dome projection: "The BMW Group Earth Lounge is not only an imposing building from the outside. The laser projection inside impresses our guests every night by its outstanding quality."

Laser all-dome projection system

The system based on Laser Display Technology (LDT) permits a full 360° x 180° projection of videos and computer images on a dome with unparalleled image definition and brilliance. The all-dome projection is composed of six image fields using six digital laser projectors which have been specially designed for spherically curved surfaces. The **Laser AllDome** projection system synchronizes the individual images and blends them into each other at the edges to give the audience the impression of a uniform, seamless image across the entire dome.

LDT – leading-edge technology for perfect images

Unique sharpness. Laser Display Technology projects images in unprecedented quality on any type of projection surface – whether flat or curved, consisting of mist screens, water curtains or other light-scattering materials.

Rich colors. Laser Display Technology uses special laser sources which mix any color required from red, green and blue laser light, permitting more colors to be reproduced than by any other kind of light source.

No pixels. Traditional image generation techniques are based on the principle of optical projection where a small image format (slide, LCD, mirror chip, etc.) is greatly enlarged by optical means. Laser Display Technology, on the other hand, writes the

Fig. 1:
Premiere for the world's largest all-dome projection by Carl Zeiss in the BMW Group Earth Lounge in August 2002.
Photos 1 to 2a: BMW Group.
Photo 2b: J.-P. Kasper

image directly on the projection surface with a laser beam.

Brilliance. The scanner's deflection technique creates a high-resolution image which appears amazingly sharper and more brilliant to the eye than the same image reproduced by other high-resolution projection systems.

Contrast. The laser technique provides a unique degree of contrast, giving the projections extraordinary depth.

Brightness. The laser bundles all emitted light into an extremely narrow pencil, without any loss.

3D impression. Due to the scanning method used, the images are sharply defined at any distance. Therefore, the eye does not focus onto the projection surface, but on the image content.

Space-saving. The laser source and projection head are installed separately and interconnected by a fiber optic light guide.

Volkmar Schorcht, Opto-Electronic Systems Business Group, Planetariums Business Unit
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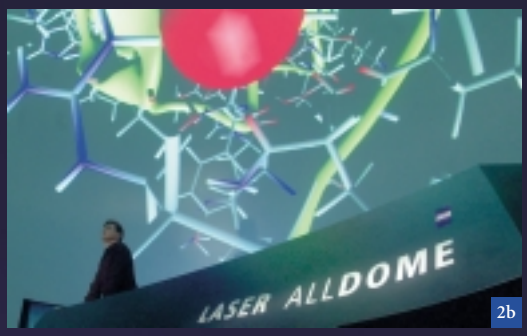
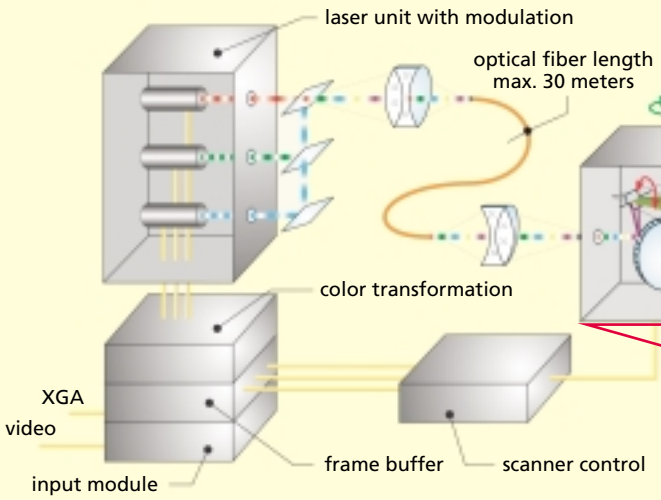




Figs 2a and 2b:
The **Laser AllDome** projection system from Carl Zeiss projects color videos and computer images with outstanding brilliance over the entire surface of a dome. The audience dips into real and virtual worlds, e.g. a molecule structure in Fig. **2b**.

Fig. 3:
Basic principle of Laser Display Technology and the scanner unit in detail.

Fig. 4:
The laser projector head.

The Right to Sight for all People in the World

In the USA, 20/20 is the term describing optimum sight. At the same time, these figures stand for the year 2020. VISION 2020's aim is to prevent people from going needlessly blind by the year 2020, if possible.

The company Carl Zeiss and the International Agency for the Prevention of Blindness (IAPB) announced in April 2002 that Carl Zeiss would support the 'VISION 20/20: The Right to Sight' initiative as a corporate sponsor. The VISION 2020 initiative is a global program of the World Health Organization (WHO) and IAPB, with a coalition of a number of international non-governmental organizations. VISION 2020's mission is to eliminate unnecessary blindness.

"Right to Sight" is a global initiative launched by different organizations together with the World Health Organization and aims to prevent unnecessary and treatable blindness by the year 2020. 80% of all cases of blindness could be prevented by suitable treatment. The goal of the initiative started in February 1999 is to prevent approx. 100 million people from going blind by the year 2020.

In addition to almost 45 million blind people, there are 135 million people who suffer from limited vision. 90% of these people live in developing countries. Blindness often puts limitations on training and education and thus blind people are a burden not only on close relatives, but also on the social community and the health care system. Unnecessary blindness causes enormous costs to the families concerned and their partners. The direct economic burden worldwide amounts to approx. US$ 25 billion. It is estimated that indirect costs are three times as high.

The main causes of blindness are cataracts, trachoma (infectious inflammation of the conjunctiva/cornea), glaucoma, retinopathia diabetica, blindness in children, onchocerciasis, xerophthalmia (deficiency of vitamin A), trauma (eye injury) and uncorrected refraction errors. The most common cause of blindness is cataracts. About half of all the blind people in the world suffer from cataracts.

Despite a comparably well structured health care system, many thousand people are blind in Germany. The most frequent causes of blindness in Germany are glaucomas and retinal changes resulting from diabetes (retinopathia diabetica). If these causes were detected in their early stages, they would be treatable and blindness could be avoided. Both glaucomas and diabetes go unnoticed by the patient as they do not develop clear symptoms for a long time. The early detection of these diseases plays an extremely important role in the fight against blindness. For this reason, it is advisable that patients who are 50 years of age visit their ophthalmologist regularly to have their intraocular pressure and visual nerve head checked. Patients suffering from diabetes mellitus should see an ophthalmologist regularly (at least once a year) to have their fundus thoroughly checked through pupil dilation.

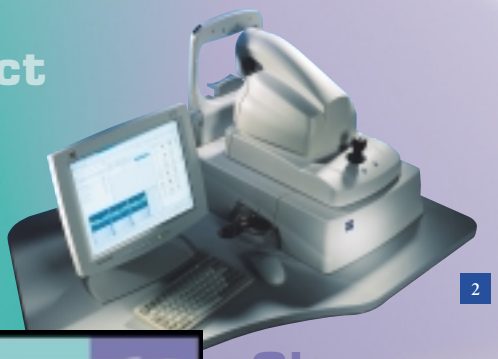
The main activity of the global Vision 2020 initiative targets the four pathologies: cataract, onchocerciasis, trachoma and xerophthalmia.

In 2002, Carl Zeiss became the first corporate sponsor of this initiative. Michael Kaschke, Board Member at Carl Zeiss, stated that he was pleased to be able to support this initiative. "Carl Zeiss was founded on the ideals of innovative science, quality and precision, and social responsibility. 'VISION 2002 The Right to Sight' is an initiative in which our funding and technology can be put to best use. We are convinced that this is a meaningful investment to support the creation of worldwide eyecare standards."

October 10, 2002 was World Sight Day supported by campaigns and events around the world.

[*www.zeiss.de*]

Good Vision is Quality of Life



The eye is our most important sensory organ. About 80% of all information from our surroundings reach us through this gateway. In our increasingly audiovisual social and work environments, loss of sight or even any visual impairment dramatically reduces the quality of life. To ensure that people also retain their sight in their old age, Carl Zeiss provides innovative instrument systems for the diagnosis and therapy of the four main pathologies.

Fig. 1:
The **IOLMaster** is used for non-contact measurement of the length of the eye and the computation of intraocular lenses prior to cataract surgery.

Fig. 2:
Stratus OCT uses the principle of optical coherence tomography to produce real cross-sectional images of the eye and to identify the causes of diseases of the fundus of the eye.

Fig. 3:
Using the **MEL 80** laser system, ametropia of the eye can be corrected using laser treatment, allowing the patient to wear either no visual aid or an aid with a lower power.

Fig. 4:
The **FF 450** fundus camera for photographic documentation of the fundus provides brilliant images and high operating convenience.

Shares with vision

Carl Zeiss has now concentrated its ophthalmological activities on the Carl Zeiss Meditec AG, Jena, with Carl Zeiss as its principal shareholder. In the past fiscal year, the company resulted from the merger of Zeiss' own and its USA activities in ophthalmology with the publicly listed Asclepion-Meditec AG, Jena. The first ever share of the Zeiss company listed on the Frankfurt Stock Exchange is called Carl Zeiss Meditec. The company with its approx. 880-strong workforce achieved proforma sales of approx. € 233 million in the year 2001 and had a 22% share of the global ophthalmology market.

A worldwide commitment to the eye

Carl Zeiss Meditec AG is one of the world's leading system suppliers for ophthalmology. Its product line includes diagnostic and therapy systems for the four principal pathologies in ophthalmology: refraction, cataract, glaucoma and retinal diseases. The product spectrum is rounded off by innovative laser systems in the field of esthetic laser medicine and dentistry.

Carl Zeiss Meditec AG has strong, long-established distribution channels around the globe. Its presence in the USA is of outstanding importance. Here, the company is excellently positioned with its own subsidiary, Carl Zeiss Meditec, Inc. (formerly Humphrey Systems).

In Japan, the second largest market after the USA, Carl Zeiss Meditec AG has also been represented by a subsidiary since October 2002.

High competence in technology

The market for ophthalmic products displays high growth potential. The increasing life expectancy of populations in all regions of the earth will remain a major agent of market growth for a long time to come. Another aspect important for a successful future is the preservation of sight in developing countries, new methods of therapy and life-style trends in developed countries. As a market leader with high technological competence and innovative product applications, Carl Zeiss Meditec AG will further expand its position in the future.

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www.meditec.zeiss.de

Innovation – The Engine of Success

Change is the key to success. This is particularly true if, whilst adapting to changing market and technological developments, a company manages to remain true to itself, its fundamental values and principles of success. After a period of radical change, Carl Zeiss now finds itself in a phase of growth and good returns.

Today Carl Zeiss is an international group with a position of global leadership in the optical and opto-electronic industry. The company's headquarters are in Oberkochen, Baden-Württemberg (Germany), and it has branches in more than 30 countries. It is represented in more than 100 countries in total. Carl Zeiss has production sites in Europe, North America (including Mexico) and in Asia. In the 2000/2001 fiscal year (year end: 30 September) the company's employees, who total around 14,200 worldwide, realized sales in excess of two billion euros. Cash flow before tax on earnings, at 226 million euros, came to 11 percent of sales. Profit after tax amounted to 110 million euros, thereby reaching a record figure for the second year in succession.

Outstanding brand

The "Carl Zeiss" brand name is extraordinarily well known, and not just among experts. It dates back to the company's founder, the university mechanic *Carl Zeiss*, who opened his own workshop for precision mechanics and optics in Jena in 1846. Even in the early days of the founder's activities, the central purpose was to serve science and technology. The commitment to innovation and outstanding scientific competence were embodied in particular by *Zeiss's* business partner, *Prof. Ernst Abbe*. With ground-breaking calculations and countless inventions, *Abbe* laid the foundation for the technological advancement and worldwide success of the company.

Science and technology

Enabling science and technology to see things that were previously invisible is, in the company's own eyes, Carl Zeiss's mission. Many users all over the world – including numerous Nobel Prize winners – have benefited from the company's achievements. With the slogan "We make it visible", which is communicated in combination with the company logo, this claim is underlined as part of a comprehensive corporate vision.

Geared towards growth

Carl Zeiss offers high-quality technological solutions for the fields of semiconductor and opto-electronic technology, life sciences and health care, eye care – including consumer and sports optics – and industrial solutions. Its focus on these growth markets places the company in an excellent position to achieve further success. Carl Zeiss is the market leader, or one of the leading players, in many of its fields of activity. It offers an extraordinarily diverse range of products and systems.

Two highly competitive business groups operate in the semiconductor and opto-electronic technology market.

The divisions Microlithographic Imaging and Illuminating Systems for Semiconductor Manufacturing Machines, Inspection Systems for Semiconductor Manufacturing, Electron-Beam Systems and Laser and Synchrotron Optics are united under the Semiconductor Technology business group, which trades independently under the name of Carl Zeiss SMT AG. The Opto-electronic Systems business group comprises objectives for cine and still photography, planetariums and instruments and systems for projection displays, spectral sensor systems and other special applications.

Life sciences is the domain covered by the Microscopy business group. For applications in this field a versatile range of light microscopes and systems for image processing and documentation, laser scanning microscopy and fluorescence correlation spectroscopy are available – supplemented by optical readers and screening systems for drug discovery in the pharmaceutical industry.

Carl Zeiss operates successfully on the growing health care market with its Surgical Products division. In the space of around 50 years, the first surgical microscope developed at Carl Zeiss has led to the development of a complete range of instruments and peripheral devices comprising solutions for all disciplines of microsurgery.

Two parts of the company operate in the field of eye care. They offer, on the one hand, instruments for the physician and optometrist, and, on the other, products for use by end customers.

Instruments relating to the area of eye examination and medical lasers represent the business of Carl Zeiss Meditec AG, a Carl Zeiss subsidiary. It was created in 2002 through the merger of Carl Zeiss's Ophthalmology division and Asclepion-Meditec AG. The company's shares are listed on the Frankfurt Stock Exchange.

The Consumer Optics business group comprises the Ophthalmic Products Division, which offers high-quality ophthalmic lenses, and the products of the Sports Optics division, which manufactures binoculars and hunting optics. Eyeglass frames and contact lenses under the Carl Zeiss brand are sold by partner companies.

For the industrial solutions market, Carl Zeiss's Industrial Measuring Technology division offers a wide range of high-precision measuring systems to meet the widely varying requirements of industry. These are supplemented by a comprehensive range of services, extending to the outsourcing of all measurement tasks.

A unique company

Carl Zeiss is a unique company with an unusual form: it is a sole tradership owned by a foundation. *Professor Ernst Abbe*, as the majority shareholder and successor of *Carl Zeiss* on the company's board of management, transferred his shares into a foundation, which he named after the company's founder. Today, the Carl Zeiss Foundation is the owner of the Carl Zeiss, Oberkochen and Schott, Mainz groups. After more than a hundred years of existence, its goals continue to be to promote the two foundation companies and the precision engineering industry, to look after the welfare of employees and their environment, and to promote science.

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The Carl Zeiss Vision

… describes the corporate philosophy and shared values of Carl Zeiss. It sets out the goals that the company wants to achieve and the paths it wants to take over the coming years.

As a pioneer in scientific optics, Carl Zeiss has always pushed back the boundaries of imagination. With its passion for first-rate performance, Carl Zeiss creates benefits for customers and inspires the world to see things in new ways. Carl Zeiss products enable science and technology to see what was previously invisible.

Promise

The new corporate slogan "We make it visible" is the promise that Carl Zeiss's technologies will lead the user into areas that were previously out of reach.

Involving employees and achieving as much transparency as possible have, from the very beginning, been the most important principles in the history of the development of the Carl Zeiss Vision. Hundreds of employees from all over the world and from all functional and hierarchical levels have made their contribution. Following intensive discussions, the results and processes are meeting with widespread approval. "We make it visible" is a promise made by Carl Zeiss as a whole in its role as an internationally operating company.

Responsibility

The Carl Zeiss Vision is not detached from social obligations. This means that the broad-based corporate targets not only include profit and growth, but also social responsibility and environmental protection among the central ideas that determine the company's actions, along with the need for mutual respect as the basis for a global company. Awareness of the fact that employees in all corners of the globe are the company's biggest asset is a direct expression of this respect and the responsibility that Carl Zeiss embraces.

Determination

New ideas and paths are only successful if they are implemented with determination. Maintaining a balance between short-term and long-term economic thinking is the key to success. Quick and decisive action, and the ability to see change as an opportunity, are just as important for Carl Zeiss as setting standards in quality and innovation. All of the company's goals are pursued with the typical Carl Zeiss qualities of persistence, commitment and a passion for technical excellence.

Carl Zeiss's standards

The key in all the company's activities is an uncompromising customer orientation. This means a high standard of quality combined with the will to be among the best in all of the business and product areas in which Carl Zeiss operates. Determination characterizes the company's actions and is inextricably linked with the responsibility embraced by all employees within the Carl Zeiss company.

www.zeiss.de

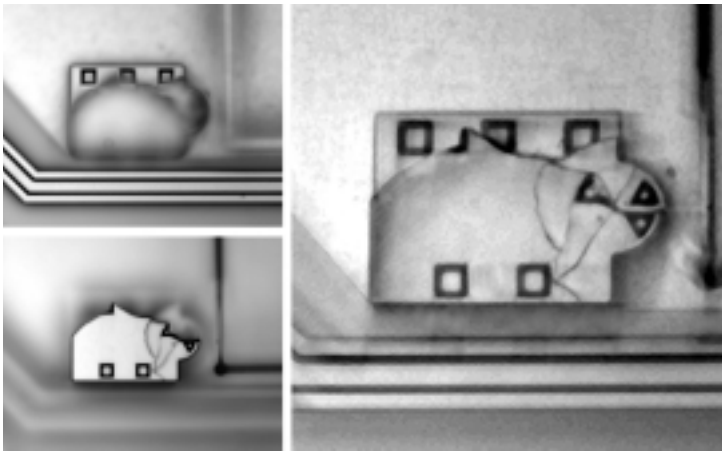
We make it visible

The Carl Zeiss VISION

The lighthouse in the logo accompanying the Carl Zeiss Vision symbolizes the values of the initiative: a guide that points the way to safety even in stormy times. It stands on stable ground, sending out its light at night and in stormy weather – not even the strongest of winds can bring it down.

Microscopy

The innovative **DeepView** technique permits a depth of focus to be achieved with conventional light microscopes which until now has been possible only with scanning electron microscopes. Micrographs of depth-extended structures available, for example, in so-called MEMS (Micro-Electro-Mechanical-Systems) components are in focus in every plane. In the development and production of such microsystems, e. g. accelerator sensors, actuators and microswitches, **DeepView** permits, in combination with the **Axioskop® 2 Mat** microscope, the fast defect recognition and failure analysis even of tilted components, without any loss of optical information. The structures and their entire depth can be visualized at a glance in quasi-real time. **DeepView** permits efficient work, high sample throughput and therefore low failure rates. The **DeepView** module is also offered for the **Axioplan® 2 imaging** and **Axiovert® 200 Mat** microscopes.

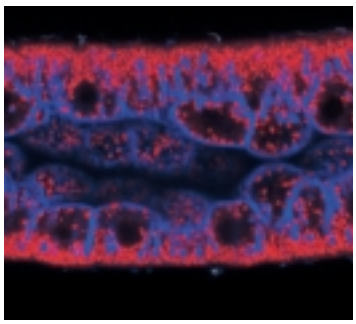


Micrograph of a MEMS anchor taken with a light microscope. Focused on the left plane (top left); focused on the top plane, distance: 12 mm (below); all planes in focus with **DeepView** (large photo).
Photo: *Daniel L. Barton*, Sandia National Laboratories (USA).

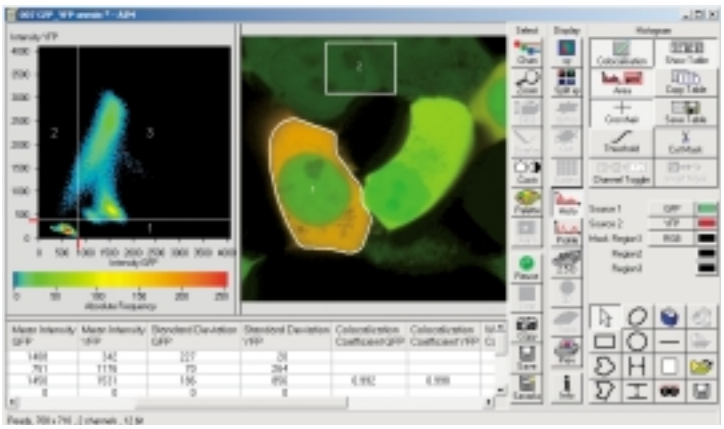
Triple fluorescence staining of a section of a mouse kidney. **Top left:** conventional fluorescence photo. **Bottom right:** photo taken with the Carl Zeiss **ApoTome®**.

The **ApoTome®** opens up a new dimension to conventional fluorescence microscopy. It is now no longer time-consuming and cost-intensive to make optical sections of biological fluorescence specimens with good image quality. The **ApoTome®** slider, which is simply inserted into the plane of the field diaphragm of the fluorescence beam path of the **Axiovert® 200** or **Axioplan® 2 imaging e** microscopes, permits optical sections to be produced very quickly and with very good quality. The image quality of optical sections of thick fluorescence specimens in particular has been markedly improved, and therefore also the quality of 3D reconstructions produced from optical sections. In addition to providing 2D and 3D images that are free of stray light, **ApoTome®** offers better image quality and definition when the thickness of the optical section measures one Airy unit.

Attractive hardware and software functions of the new **LSM 5** laser scanning microscopes further increase the user-friendliness of quantitative confocal image recording and analysis. For example, quantitative colocalization experiments are made easy and reliable, an enhanced physiology package improves experiments with living cells, and a blue 405 nm diode laser is available as an easy-to-use alternative to UV lasers. The comprehensive colocalization tool provides a complete set of quantitative data with colocalization coefficients and correlation parameters. These are interactively linked to a threshold function and can be directly extracted from image regions. The enhanced physiology package permits convenient image acquisition and complete concentration calibration in experiments with living cells. A blue 405 nm diode laser is offered for the visualization of DAPI and FRET images and for experiments with fluorescent proteins. The new functions can be integrated in existing **LSM 5** microscopes via hardware and software modules.



Mitochondria (blue) and cell membranes (red) in a living salivary gland of a fly were dyed with the TMRE and FM 4-64 markers, which were then separated by Emission Fingerprinting with Automatic Component Extraction (ACE) on the **LSM 510 META**.



The quantitative colocalization tool of the **LSM 5** with interactively linked scattergram, image display and data table.

Release 3.2 is a new software version for the **LSM 510 META** laser scanning microscope which provides new functions dedicated to Emission Fingerprinting, the unique method for the separation of fluorescence dyes with overlapping emission spectra. The new Online Fingerprinting mode permits both separation of overlapping fluorescence signals with the aid of the **META** detector simultaneously with image acquisition and the direct visualization of results. This is an ideal solution for fast specimen evaluation and for experiments with living cells. Automatic Component Extraction (ACE), an intelligent software algorithm, complements the existing interactive selection of reference spectra for Emission Fingerprinting. Using statistical methods, ACE automatically searches for the component spectra in experimental raw images, thus providing an additional starting point for separating spectrally overlapping emission signals in cases where reference spectra cannot be collected from control preparations. Added to existing systems by a simple software upgrade, the new functionality makes Emission Fingerprinting with the **LSM 510 META** even more transparent, versatile and easier to use.

M2 Fl S fluorescence equipment for **Stemi® SV** stereomicroscopes, the ultimate stereomicroscope for GFP fluorescence microscopy.

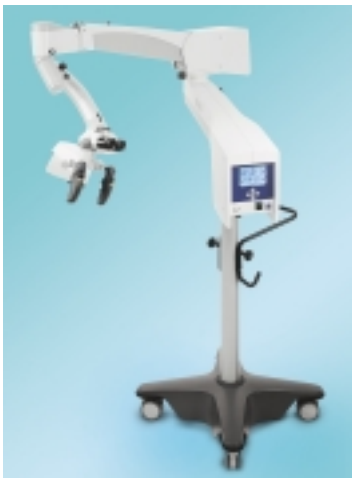
Especially in molecular biology and genetic engineering laboratories, the **Stemi® SV** fluorescence stereomicroscope has become an established tool for the observation and investigation of growth processes of living organisms. The **M2 Fl S** equipment now further extends the application range of this instrument, i. e. two microscopic techniques have been combined in a single instrument. In addition to the stereo mode with the familiar three-dimensional images and large object fields, a further mode now provides magnifications up to 660x by simple switching of the nosepiece. Both modes permit the fluorescence contrast technique and, if required, the transmitted-light technique over the entire magnification range. A special filter turret facilitates the fast change between maximally four different fluorescence filter blocks. For examinations in the high-resolution area, two different objectives (10x/0.45 and 20x/0.42) are available.

Surgical Products

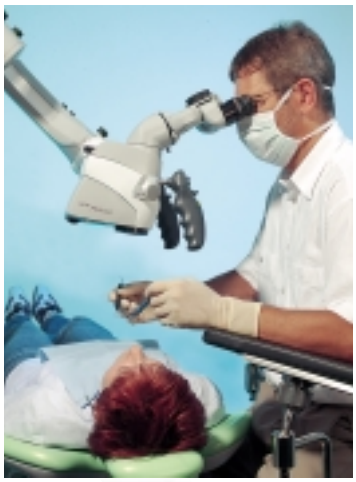
The new **INTRABEAM** system technology allows direct irradiation of the tissue in the wound cavity in the immediate vicinity of the removed tumor directly after the surgical procedure. New, intraoperative therapy possibilities are becoming available. The system is already being used as a matter of routine in 20 hospitals around the globe. The convenient irradiation system – a lightweight, miniaturized X-ray source from the Photoelectron Corporation – can be utilized in any OR without difficulty. A spherical applicator (dia. 1.5 to 5 cm) which encloses the tip of the hollow anode is placed directly in the wound cavity and fills out the entire tumor bed, i. e. the tumor bed and the bordering tissue are irradiated from the inside with a high dose of radiation. This highly dosed, single irradiation is considerably more efficient than radiotherapy using low individual doses applied from the exterior, as the biologically effective dose is markedly higher. 90 percent of all recurring tumors occur in the direct vicinity of the original tumor. The reduction in the duration of the radiotherapy after surgery which this permits is the subject of an international study in four leading competence centers in London, New York, Perth and Mannheim, where intraoperative radiotherapy has already been successfully performed. This therapy will allow minimization of cost-intensive, follow-up radiotherapy in the long term. **INTRABEAM** has been granted FDA and CE approval for use on the entire body and can be used across the board in all disciplines (e. g. chest, brain, colorectal and bone).

Ease of use, optical brilliance and perfect integration are the outstanding features of the **OPMI® Sensera/S7 System**. Whether it is used for applications in the neck, throat or ear, the **OPMI® Sensera** offers the physician super mobility and precise user guidance. It quite simply leaves nothing to be desired. Depending on the procedure to be performed, a coobservation device and a laser can be attached without difficulty. For the very first time, a **Varioscope** system has been integrated into an ENT microscope from Carl Zeiss – the constant changing of the objective lens is now a thing of the past, and the system can be set to the required working distance at the press of a button. The fully integrated xenon illumination with daylight characteristics, the video camera and internal routing of the cables are examples of how the many benefits of the system are very noticeable, but not visible to the surgeon and the surgical team.

The **OPMI® PROergo** is the perfect equipment for practitioners who wish to offer their patients innovative dentistry. Maximum mobility and flexibility, combined with legendary Zeiss optics and a truly amazing video solution, number among the many outstanding features offered by the successor to the former **OPMI® PRO magis** dental microscope. Other convincing benefits include a comfortable, upright seated posture for the dentist – without backache – even during long periods of treatment, and precise, continuous and effortless positioning of the system. Three suspension systems for floor, ceiling or wall installation allow optimum integration into the dentist's office.



OPMI® Sensera/S7 System surgical microscope.



OPMI® PROergo dental microscope.

INTRABEAM – Increasing the quality of life for cancer patients using innovative, intraoperative radiotherapy.

Sports Optics

The Zeiss **Diadem®** will allow you to experience what is happening on the theater stage with different eyes – and not only for performances of classical plays, but also for the circus, musicals and open air concerts. This stylish accessory is simply ideal for any occasion. Its excellent, high precision optics incorporating the entire experience of Zeiss, the sophisticated, distinctive design, and its superb craftsmanship make this binocular truly unique.

No matter where you are sitting in the theater, the 3.6x magnification of the **Diadem®** will let you see everything in close-up.

The new **ClassiC Compact 8x20 BT*** and **10x25 BT*** pocket binoculars will be your perfect companion when you are traveling. They can be folded together in next to no time and fit into even the smallest pocket without difficulty.
Like their "big brothers" in our product line, these small, light and very robust pocket binoculars provide excellent image quality, razor-sharp definition, and breathtaking brilliance, color fidelity and transmission thanks to the **T*** multicoating. These exclusive optics are optimally protected by an elegant housing made of a climate-proof, fiber-reinforced synthetic material. Special eyepieces guarantee a full field of view, even if you are wearing prescription eyeglasses or sunglasses.

It is ideal not only for watching, but also for capturing those precious moments in life: The new Zeiss **camera adapter** converts Zeiss **spotting scopes** into super telelenses with focal lengths of 770 mm and 1,000 mm. Any SLR camera can be mounted on this **adapter** with the appropriate commercial **T2 ring**. No matter whether you want to take horizontal or vertical format photos, you can turn the camera in the **adapter** any way you want. The Zeiss **camera adapter** fits all Zeiss **Diascope 65 T* FL** and **85 T* FL spotting scopes**.

Camera adapter for the **Diascope® 65 T* FL** and **85 T* FL** spotting scopes.

Ophthalmic Products

An attractive design and modern material are the outstanding features of the new **STMS®** system carrier (Support Titanium for Magnifying Systems). The use of pure titanium guarantees not only low weight, but also maximum skin-friendliness, and hence makes a decisive contribution to the wearing comfort of the system. Its single-piece bridge-element gives the carrier exceptional dimensional stability and makes it extremely torsion-free. A good fit of the system is ensured by the proven silicone saddle bridge, but individual, comfortable soft pads can also be fitted. Eight different frame sizes and the possibility of equipping the frame with hook-type or straight temples guarantee optimum adaptation of the system to the needs of each individual user. Although it has been developed for low vision patients, the **STMS®** system carrier is also suitable for use in medicine and technology. It has been designed in such a way that it can accommodate all Galilean and Kepler telescope systems from Carl Zeiss.

The new **Compact 10 x 25 BT*** and **8 x 20 BT*** pocket binoculars from Carl Zeiss.

STMS® system carrier.

The head-worn loupe **KF titanium** is used for binocular stereoscopic near vision in medical and technical applications. Since January 2002 it has featured a new optical system with a 10% increase in its fields of view compared to previous systems. This allows good orientation, even with high magnifications, and guarantees a full overview of the work area. The optical system is available in various magnifications and working distances, and the system carrier in various frame sizes. High-eyepoint eyepieces for eyeglass wearers allow the system to be worn in front of the frame which can also be glazed with lenses of practically any prescription.
The protective devices for the objective lenses have been integrated into the housing, ensuring that the optical system is optimally protected against damage. The wearer benefits from a marked reduction in weight thanks to the new **STMS®** system carrier made of pure titanium. The head-worn loupe **KF titanium** (previously approx. 155 g) now tips the scales at a mere 135 g.

Head-worn loupe **KF titanium**.

Masthead

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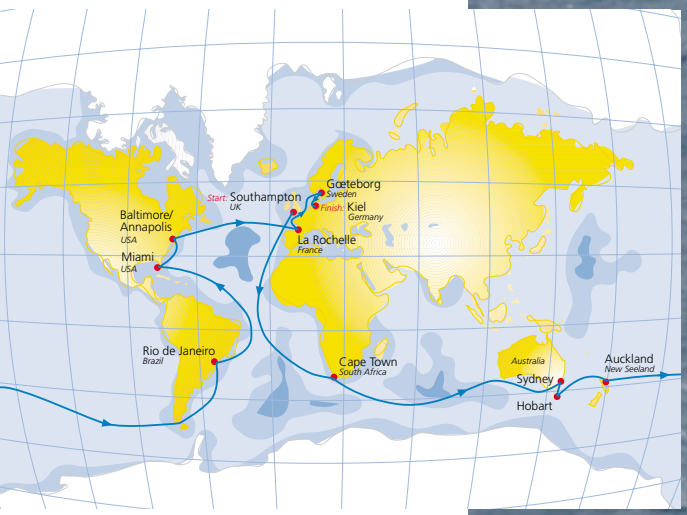
The Magazine from Carl Zeiss
Innovation



Cover photo:
The yacht illbruck – winner of the "Volvo Ocean Race Round the World 2001 – 2002". Photo taken on the third leg from Sydney to Auckland via Hobart.

Like all other yachts entering the race, the illbruck had three Carl Zeiss spectrometers on board for capturing environmental data.

Outside back cover:
Route and leg map of the "Volvo Ocean Race 2001 – 2002" starting in Southampton and ending in Kiel.