P012-E936

SHIMADZU

INNOVATION

SHIMADZU INFORMATIONAL FORUM

2004
No.36

Sports and Science

New training systems scientifically developed for individual athletes improve the performance of athletes

A Paradigm Shift in X-ray Imaging

- X-ray Imaging System Equipped with Direct-conversion FPD (Flat-panel Detector)
- Whole-body PET System

Quality Customer Support Increases the Value of Our Products

Shigehiko Hattori, President & CEO of Shimadzu Corp.

Total Solutions for Meeting European Environmental Regulations

The Fruit of Collaboration between Academia and Industry

An "Ultra-Small Electron Microscope" Born from Carbon Nanotubes

Interview

Keeping "Eyes" on the Path to Proteomics

Osamu Nishimura & Koichi Tanaka of Shimadzu Corp.

Who is beyond the Ocean

Shimadzu Research Laboratory (Europe) Ltd.

Sports and Science

New training systems scientifically developed for individual athletes improve the performance of athletes

The Olympics will be held this year.
This summer, Athens will be the center of world attention.
Japanese expect Japanese athletes to perform well, especially swimmers.
Japan used to be a swimming powerhouse though has not been one for many years now. Although Daichi Suzuki won the gold medal at the Seoul Olympics in backstroke and others have won medals before, Japanese swimming has not captured the attention of people worldwide for a long time.
However, this year's Olympics should showcase some great Japanese swimmers.
Breaststroke specialist Kosuke Kitajima and some other Japanese swimmers are expected to win medals.
We asked veteran Daichi Suzuki how Japanese swimming has changed over the years.

Expectations for Japanese swimmers

Performances of Japanese swimmers have been remarkable lately.
Japanese swimmers won four medals (silver or bronze) at the Sydney Olympics, and they won six medals at the Barcelona World Swimming Championships held last August. The most standout achievement at the championships was winning the bronze medal in the men's 400 meter medley relay for the first time. Although it was the result of the Australian team being disqualified in the preliminaries, it was still a first in Japanese swimming history. People in Japan now expect a lot from their team at the Athens Olympics.
The swimmer who is attracting the most attention these days is Kosuke Kitajima, who set two new world records and won two gold medals at the championships. He is still in great condition and the subject of media attention with hopes high for a memorable performance in Athens.

Athletes that are reviving Japanese swimming

Japanese competitiveness in swimming did not develop along a straight trajectory.
Before WW II, swimming was Japan's specialty. Japan won five gold medals at the Los Angeles Olympics in 1932 and

Kosuke Kitajima holds the world record for the 100 and 200-meter breaststroke (as of February 2004).

four at the Berlin Olympics in 1936. Japanese swimmers were regular members on the podium until the Rome Olympics in 1960.

However, at the Tokyo Olympics in 1964, Japanese swimmers only won one bronze medal. These results were devastating and Japanese swimming went into a long decline. Japanese swimmers have won only six medals since through the Atlanta Olympics in 1996.

During this period, Daichi Suzuki made a big splash by winning a gold medal in the 100-meter backstroke at the Seoul Olympics in 1988.

Mr. Suzuki outdistanced his competitors by using the so-called "Vassallo" technique (diving for a long distance after starting). His gold medal was very special and made Japanese people exuberant because Japan had not won any medals in swimming at the previous three Olympics.

Training programs catered to the individual

Mr. Suzuki's performance was supported by advanced training methods.

In the past, all Japanese swimmers training for the Olympics lived and trained together. Coaches often told athletes to train themselves as hard as possible and to overcome physical pain with a strong fighting spirit.

However, foreign countries came up with more effective training methods while Japan was still trying to win by spiritual power. These new training methods were catered to each individual athlete and developed based on scientific analysis.

Each person has a different type of body, muscles, and oxygen exchange capacity. There should be adequate training programs that suit each individual's characteristics.

According to Mr. Suzuki, there are many different coaching methods in the US as compared to the Japanese method of teaching everyone the same way. Some US coaches let athletes swim as they like and maximize their strong points while others fine tune technique. As a result, the US has a strong team with various types of swimmers. He also says that former Japanese training methods were responsible for creating many average athletes, but few stellar ones.

At the Olympics, differences in training methods lead to great differences in performance.

Mr. Suzuki and his coach concentrated on mastering the unconventional "Vassallo" technique. The "Vassallo" technique was considered to be unorthodox because diving for a long time places a burden on the respiratory and circulatory systems and reduces endurance, even though it increases swimming speed. Nevertheless, they thought it would be effective. Before the final at the Seoul Olympics, they analyzed competitors' heat results and conditions and boldly decided to increase the diving distance. As a result, he won the gold medal. There is no doubt that his individually catered training program was key to his gold medal winning performance.

Science to support sports

Mr. Suzuki's training was indirectly supported by scientific analyzing methods.

For example, there is a device called a lactate analyzer that measures lactic acid content in muscles. Lactic acid content increases when muscles are tired. Measuring the content helps to determine the perfect amount of exercise and rest and also to establish guidelines for training.

Profile

● Daichi Suzuki

Born in 1967. Won the gold medal in the 100-meter backstroke at the Seoul Olympics in 1988 when he was a student of Juntendo University. Coached Harvard University's swimming team. Currently, he is an instructor of Juntendo University's School of Sports and Health Science and coach of the university's swimming team. He is also a JOC athlete committee member and Olympians Association of Japan director. *www.daichi55.com*

Improved training environments enhance athletic ability

Swimming pools with running currents are very important for training. In this type of pool, maximum oxygen intake, which greatly influences athletic performance, can be measured while staying in one position.

During a race, athletes fully exert all of their muscles for more than one minute. The high endurance required to sustain this effort depends on adequate oxygen intake.

Maximum oxygen intake (VO_2 MAX) is measured to evaluate each athlete's oxygen intake capacity. Swimming pools with currents allow measurements to be conducted while athletes are actually swimming.

Mr. Suzuki and his coach used these advanced scientific methods, established training programs that best suited him, and systematically implemented a weight training regimen in order to improve muscle strength.

Mr. Suzuki says "Only a few athletes had implemented a weight training regimen at that time. Coaches of some teams simply demanded athletes to swim, swim, and then swim some more."

He was the first swimmer in Japan to use scientifically devised training methods. His excellent performance at the Seoul Olympics showcased the possibilities of using new types of training programs.

Over the course of the past 16 years, personal scientific training methods have become standard.

Mr. Suzuki said, "Until 1996, all swimmers lived and trained together leading up to the Olympics. Yet at the Sydney Olympics, athletes trained by themselves. This led to better performances."

Olympic gold medals won by Japanese swimmers

1928 Amsterdam	200-meter breaststroke	Yoshiyuki Tsuruta
1932 Los Angeles	100-meter freestyle	Yasuji Miyazaki
	1,500-meter freestyle	Kusuo Kitamura
	100-meter backstroke	Masaji Kiyokawa
	200-meter breaststroke	Yoshiyuki Tsuruta
	800-meter relay	Men's team
1936 Berlin	1,500-meter freestyle	Noboru Terada
	200-meter freestyle	Tetsuo Hamuro
	800-meter relay	Men's team
	200-meter breaststroke (women)	Hideko Maehata
1956 Melbourne	200-meter breaststroke	Masaru Furukawa
1972 Munich	100-meter breaststroke	Nobutaka Taguchi
	100-meter butterfly (women)	Mayumi Aoki
1988 Seoul	100-meter backstroke	Daichi Suzuki
1992 Barcelona	200-meter breaststroke (women)	Kyoko Iwasaki

Changes in athletes' environment

There are other factors that are advantageous to today's athletes.

First of all, many companies financially back athletes. They sponsor athletes to improve their corporate image and some companies even offer training facilities.

Mr. Suzuki said, "When I was a university student and graduate school student, I drove over an hour on the highway to a swimming pool to train. I envy today's athletes because they can train under much better conditions (laugh)."

Another factor is people's improved interest in sports. Lifestyles of top athletes have become the subject of media coverage because people are interested in them.

Mr. Suzuki said, "It is huge that today's athletes can choose by themselves how to train and live."

The first WOA director from Asia

Mr. Suzuki was selected as one of nine directors of the World Olympians Association last November. He received the second highest number of votes among 24 candidates. He is the first director of the association from Asia.

He said, "All the directors selected are national heroes and legends. It is a great honor to be a part of this group. I would like to work hard so that Japan will gain a greater voice in the sporting world."

Mr. Suzuki working hard in his university office During the interview, many students came to his office to meet him.

WOA is an international organization that consists of Olympians. They are all ex-athletes with Olympic experience though their nationality, age, and the Olympic events they participated may be different. The main goals of the organization are to increase the recognition of WOA and invigorate the sporting world.

Mr. Suzuki said, "Sports move people and even motivate them to live. We should not forget that sports have that strong an impact on society."

Life after winning a gold medal

Mr. Suzuki has more dreams.

He said, "What interests me the most now is how we can provide jobs for athletes after their retirement. I was lucky to become a coach and instructor at this university but I know many ex-athletes suffer because they are unable to find a suitable job. Without job opportunities, fewer and fewer people will continue their sport careers or be interested in becoming a hard-training athlete."

As a college instructor, coach, and WOA director, Mr. Suzuki has a very busy life.

He said, "I would like to mix my own experiences with new theories and technology and apply them to actual training for athletes. I should also show people that my life really began after winning a gold medal."

A laboratory that can create hypoxic conditions similar to those found at an altitude of 5,000 meters. A study to learn about the influences of training at high altitudes is conducted.

Actively supporting athletes by applying the most advanced science

Japan Institute of Sports Sciences

The Japan Institute of Sports Sciences supports athletes by utilizing the latest technology and the results are attracting people's attention.

"Double the medal take by the 2012 Olympics"

Using this phrase as a slogan, the Ministry of Education (currently the Ministry of Education, Culture, Sports, Science and Technology) declared its intention to promote sports in 2000.

Japan took 3.5 percent of the medals at the Montreal Olympics in 1976 when Japan had a strong volleyball team. However, they only took 1.7 percent at the Atlanta Olympics in 1996. Even at the Sydney Olympics where swimmers did very well, the rate was lower than 2.0 percent. Japan has about 2.0 percent of the world's population and though Japan boasts the world's second largest economy, it can still be considered to be a developing nation with respect to sports, because its medal acquisition rate is lower than its percentage of the world population.

Mr. Toshio Asami,
the head of the Japan Institute of Sports Sciences

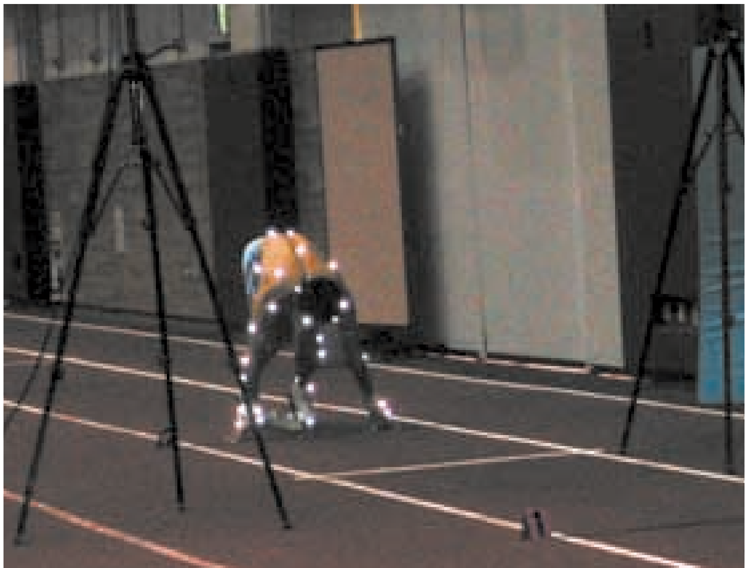
The "Japan Institute of Sports Sciences" (Kita-ku, Tokyo) was established to change this situation. The institute thoroughly supports the strengthening and training of national team athletes from scientific, medical, and information-oriented perspectives.

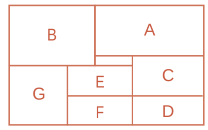
The training site is as large as a soccer field. There is a seven-story building with a basement. In this building, there are special swimming pools for training and synchronized swimming; training areas for wrestling, fencing, boxing, weight lifting, and gymnastics; a gym with two basketball courts; and weight training equipment.

Most ordinary exercising facilities have these features, though the institute provides much more. There are 80 accommodation rooms on the fifth and sixth floors, 72 of which can be set at hypoxic conditions similar to those found at an altitude of 3,000 meters. The training gym also can be set at hypoxic conditions similar to those found at an altitude of 3,500 meters. In short, athletes can experience training at high altitudes without having to actually travel to higher altitudes.

Japan Institute of Sports Sciences in Tokyo

There are even more great features. The Department of Sports Science has instruments to measure the functions of the respiratory and circulatory systems as well as the muscular and nervous systems. The department also has a temperature/humidity laboratory where people can learn about changes in their bodies





Caption

A
One side of the swimming pool for synchronized swimming is made of reinforced glass enabling observation of athletes in the water. A coach was very excited to see this and said, "This is exactly what I wanted."

B
Sensors are placed on an athlete's body to record his motions. The athlete's data can be analyzed and compared with data for other athlete's or his own best results to find their best possible form.

C
The institute has a physician, orthopedist, and dentist. It also has blood/urine testing equipment as well as x-ray and electrocardiogram systems in order to accurately evaluate athletes' physical conditions and give precise advice.

D
Video editing and analyzing laboratory. In addition to editing of video pictures, games recorded on-site or broadcasted at BS/CS TV programs are analyzed to improve athletes' performance.

E
A large treadmill with a 3x4 meter running space. It can be used for cycling training as well because speeds can be set up to 60 km/h. Experiments with more than one athlete can be carried out.

F
An MRI system is used to measure cross-section areas of athletes' muscles, etc.

G
Fitness checking. Body structure, physical makeup, aerobic/anaerobic capacities, and muscle strength can be measured.

at high-temperature/humidity conditions, an image recording/analyzing device to record athletes' fine movements with a high-speed camera, and instruments to analyze blood and evaluate immune functions.

The institute can be thought of as a facility that strengthens athletes at the cellular level.

With x-ray, CT, and MRI systems, the institute functions as a cutting-edge sports medical facility. It also can collect images and numeric data of athletes all over the world and analyze it. The institute has everything that is necessary to win except for the athletes themselves.

Mr. Toshio Asami, the head of the Japan Institute of Sports Sciences, said, "People wanted a facility like this even at the Tokyo Olympics. However, people in Japan did not prioritize sports so it took a long time to make scientific approaches to sports."

The establishment of a national sports facility has long been needed to enhance the international competitiveness of Japan's athletes. All countries known as "sports powers" have national facilities that function as a base of sports medicine and science. Daichi Suzuki said, "All countries that have these types of facilities have successfully improved their athletes' abilities."

Mr. Asami also said, "We work behind the scenes. I want athletes and their coaches to use the facility effectively and achieve great results. We will do everything to help them."

The breaststroker Kosuke Kitajima mainly trains here when in Japan. Hopefully many great athletes will train and be nurtured here in the years to come.

A Paradigm Shift in X-ray Imaging

X-ray Imaging System Equipped with Direct-conversion FPD (Flat-panel Detector)

Shimadzu has been involved in the development of X-ray imaging systems for over a century. Last year, it developed the "Direct-conversion FPD (Flat-panel Detector)" and, in so doing, realized a remarkable step forward in the quest for higher resolution and lower radiation dose. (The direct-conversion FPD was developed in collaboration with Sharp Corporation and Shindengen Electric Manufacturing Co., Ltd.) X-ray imaging systems equipped with direct-conversion FPDs have already been released in the Japanese market and have received much attention from interventional cardiology professionals and other radiological imaging institutes.

Providing Dynamic X-ray Imaging with Quality Equivalent to that of Film

A perennial issue for doctors and technicians involved in medical X-ray imaging has been how to reduce the burden on the patient by improving resolution and reducing radiation dose. Shimadzu has developed a large number of X-ray imaging systems over the past 100 years. With each new system it has created new technology promoting the evolution of diagnostic imaging systems. In recent years, amidst a trend of digitalization, Shimadzu has created highly acclaimed fluoroscopy and cardiac/vascular systems equipped with CCD cameras. In October last year, Shimadzu released an epoch-making new product in its imaging system equipped with a direct-conversion FPD (flat-panel detector). This system offers superior resolution equal to that of film which can be obtained for both still and dynamic images.

Converting X-rays Directly to Electric Signals

The direct-conversion FPD developed by Shimadzu has two noteworthy features. The first is that it is digital, and the second is that the conversion method is direct rather than indirect.

The advantages of being digital include

The "DIGITEX Safire HC" cardiovascular X-ray diagnostic system equipped with direct-conversion FPD is packaged with a ceiling-mounted C-arm. A system with a floor-mounted C-arm, "DIGITEX Safire HF," is also available.

the elimination of the need to develop films, and the ability to allow real-time image observation.

The difference between the indirect-conversion FPD and the direct-conversion FPD is as follows. The role of the FPD in an X-ray imaging system corresponds to the lens and film in a camera. In place of a lens and film, X-rays are received by an array of detector elements and converted to electric signals. Whether this conversion is direct or indirect is what differentiates the two types of detectors.

Indirect-conversion FPDs can be developed by combining pre-existing technologies and several manufacturers have already released systems based on this method. With indirect conversion, the image obtained with the X-rays is first received by fluorescent material; the X-rays are converted into light, which is received by an array of photodiodes where it is further converted to electric signals. In other words, the indirect-conversion method can be thought of as consisting of 4 stages: the X-rays that pass through the patient are received; the X-rays are converted to light; the light is received; and the light is converted to electric signals. As with the photocopying of documents, it is impossible to prevent degradation of the resolution at each stage.

The direct-conversion FPD developed by Shimadzu, however, incorporates an X-ray detecting layer that can handle the X-rays that pass through the patient without prior conversion to light. This allows direct conversion to electric signals and ensures that the drop in resolution is kept to an absolute minimum. This method had for some time been considered an ideal way of improving resolution but was dismissed as posing too many technical problems. Shimadzu, however, recognized that the indirect-conversion method was insufficient for meeting the needs of modern medical facilities and embarked on the development of the direct-conversion FPD. Last year's sales release in Japan represented the fruit of these efforts.

Greatly Improved Visibility

In October last year Shimadzu released the world's first cardiovascular X-ray imaging system*1 equipped with a direct-conversion FPD, DIGITEX Safire. It has been well received, earning high praise for its clinical performance.

In interventional cardiovascular treatments, angina and myocardial infarction are treated by inserting catheters into narrowed blood vessels and scraping away the plaque inside arterial walls, or by inflating the blood vessels with balloons. This is facilitated by injecting contrast medium into the blood vessels and determining the appropriate direction in which to move the catheter by viewing dynamic X-ray images of the medium. Naturally, in order to ascertain which blood vessels have narrowed or to locate the tip of the catheter, a high resolution is demanded of X-ray imaging systems. This is where the direct-conversion FPD proves its worth. Images obtained by conventional I.I./CCD camera system and direct-conversion FPD are shown below.The high resolution of 150 μm/pixel and the low noise level ensured by the direct-conversion method significantly improve the visibility of fine blood vessels, which are difficult to see with either the indirect-conversion FPD or the conventional I.I.*2 systems.

"Visibility of stents*3 and microcatheters

Test image obtained by conventional I.I./CCD camera system

Test image obtained by direct-conversion FPD

Tsunekazu Matsuyama
Director of Shimadzu Corporation
General Manager, Medical Systems Division

Profile

in blood vessels, which were hard to make out with the conventional I.I. system, has greatly improved. It seems that we can anticipate many benefits as a result, such as shorter examination times, reduced radiation dose and lower volumes of contrast medium," says Tsunekazu Matsuyama, General Manager, Medical Systems Division, Shimadzu Corporation.

Creating New Possibilities in Interventional Cardiovascular Therapy

This system offers a wide 9″×9″ field of view without peripheral distortion thanks to the flat-panel design. Even though the I.I. offers a circular field of view with a 9-inch diameter, it is impossible to prevent peripheral distortion (see photographs below). The FPD produces clear, undistorted images over the entire field.

"This means that the catheter operation time can be shortened. This reduces both the burden on the doctor and the invasiveness on the patient," says Matsuyama.

Shimadzu is currently developing a 17″×17″ direct-conversion FPD. When this is completed, it will be able to cover the entire chest region. Its application to general X-ray imaging is keenly anticipated.

Contributing to Society through Healthcare using X-rays

"At present, Japan's medical technology ranks as one of the most advanced in the world and high-level medical treatment is available to everybody. On the other hand, as the population continues to age, healthcare costs continue to increase. In order to reduce these costs and improve the level of patient care, major reforms of the health service are unavoidable."

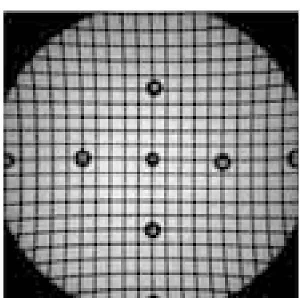
"Here at Shimadzu, in addition to developing cardiovascular X-ray systems, we plan to use the direct-conversion FPD in a variety of X-ray diagnostic systems. If these systems become widely used, the digitalization of images will become possible at medical facilities that still use mainly film. We believe that this will encourage the use of IT in the field of medical imaging and advance teleradiology technology based on digital image communications, thereby reducing differences in medical expertise levels among regions and enabling faster diagnosis and treatment," explains Matsuyama.

Shimadzu's X-ray technology has a history of more than 100 years. Its accumulated knowledge and technological framework as well as consideration of the needs of medical facilities and patients have led to the birth of the direct-conversion FPD.

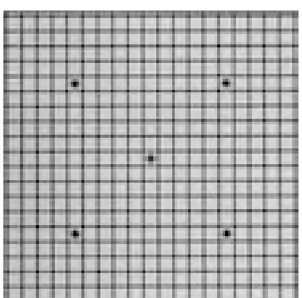
*1 **Cardiovascular X-ray imaging system :**
By injecting a contrast medium into the blood vessels, the blood vessels and blood flow around the heart can be observed in dynamic images. This system is used to check for disorders, such as coronary arterial stenosis, and to perform procedures for expanding narrowed blood vessels.

*2 **I.I. :**
"I.I." stands for "image intensifier" and is the vacuum-tube device traditionally used to produce fluoroscopic images.

*3 **Stent :**
A special wire-mesh tube used to expand a narrowed blood vessel from the inside.



9-inch I.I.

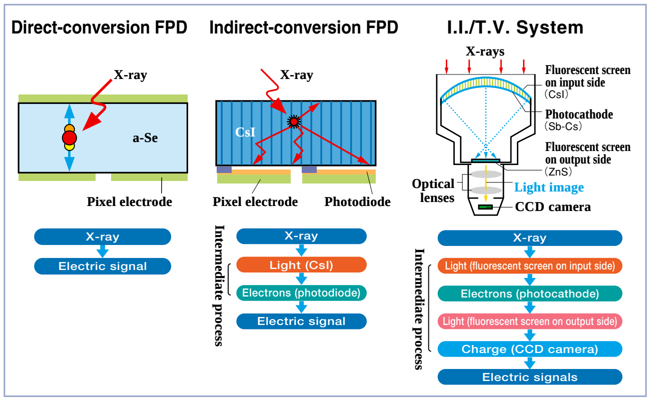


Direct-conversion FPD (Safire)

Mechanism of Direct-conversion FPD

Direct Conversion of X-rays to Electric Signals
Innovative Technology That Minimizes Deterioration in Image Quality

With the conventional I.I., there are several conversion processes between the incidence of X-rays and the creation of electric signals for displaying the image, and it is impossible to prevent loss of information and generation of noise. Even the indirect-conversion FPD offers no major improvements in this respect. The direct-conversion FPD, however, converts X-rays directly to electric signals in the conversion material (amorphous selenium). This optimizes the conversion process and reduces deterioration in image quality to the absolute minimum.



Xray Imaging System Equipped with Direct-conversion FPD Supports the Latest Treatment

Striving for Patient-centered Treatment

Hokuto Cardiovascular Hospital (Sapporo City, Hokkaido Japan), which carries out advanced, specialized treatments for heart disease, currently uses two DIGITEX Safire systems. Dr. Hideki Abe, Chairman of the hospital and head of its cardiology department, abides by a personal philosophy of "patient-centered treatment" and has carried out over 2,000 stent procedures. We asked him about his impressions of the Safire system and his visions for the future of community healthcare.

A Powerful Weapon in the Fight against Heart Disease

We moved to the present site in January this year in order to expand our services by opening a heart-surgery department. At the same time, we purchased and installed Shimadzu's DIGITEX Safire system, which is equipped with a direct-conversion FPD. Although I had seen the visual clarity with prototypes, I was still very impressed. The image quality was significantly better than that of the I.I. (image intensifier) we had been using and even fine blood vessels could be clearly visualized.

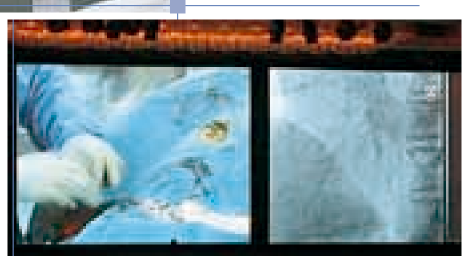
There is no peripheral distortion or blurring and no halation, making it easy to see fine blood vessels. The thing that surprised me most was that the stent could be seen clearly without injecting a contrast medium. The most common treatment in current interventional cardiology is the prevention of restenosis of the blood vessels using stents. Positioning the stent has always been very difficult but since we installed the Safire system, it has become possible to place the stent at the exact position with just one test shot of contrast medium. As a result, both the radiation dose to the patient and the amount of contrast medium injected can be significantly reduced. The amount of contrast medium is typically 20% less than before. We can also anticipate greater success with restenosis prevention.

Because fine details can be seen with the Safire system, some conditions that would usually have necessitated surgical treatment can now be treated with less invasiveness. This means that the burden on patients can be reduced and makes the Safire system a powerful tool for medical practitioners.

A new treatment using a "drug-eluting stent"*1 is due for approval in Japan this autumn. The introduction of this treatment is expected to further reduce the angina recurrence rate and heralds the start of a new era in interventional cardiology. Accurate stent positioning is very important with this treatment. It is very encouraging to know that we will be able to implement this treatment with the help of such clear images.

Dr. Hideki Abe
1980: Graduated from Sapporo Medical University; 2000: Appointed Chairman of Hokuto Cardiovascular Hospital. Certified by the Japanese Society of Internal Medicine; registered as a specialist with the Japanese Circulation Society; panel member at the Japanese Society of Interventional Cardiology and executive officer for the Hokkaido region; director at Japanese Association of Cardiovascular Therapeutics; visiting professor at the affiliated hospital of Fujita Health University's School of Medicine Hospital; professor emeritus at Dalian Central Hospital in China.

Hokuto Cardiovascular Hospital
Kita 25-jo Higashi 20-7-1, Higashi-ku, Sapporo City, Hokkaido, Japan



Hokkaido Education Live Demonstration, Jan.2004

High Praise for Shimadzu's Support Framework

In a sense, the catheterization lab is a battlefield. We are fighting disease in order to protect the patient. If our "weapon" is broken, we are no longer able to fight. It is therefore very important for clinicians to know that the equipment is durable and stable. Nevertheless, the possibility of malfunction cannot be completely avoided with any machine. It is important to know what to do when the machine malfunctions and what kind of help is available. In this area, Shimadzu is a company worthy of special mention. Whenever there is a problem, a technician comes straight away and, in cases where lengthy repair work is required, continues working throughout the night so that the equipment is in perfect working order for the next day. I very much appreciate this level of response.

Establishing Regional Coordination

Although Hokkaido is a very large area, the number of doctors and medical facilities here is very limited. With the aim of creating a network of cardiovascular specialists working in the region, for the past 5 years I have been conducting demonstrations dubbed "Hokkaido Education Live".

At this year's demonstration, which was held at a hotel in Sapporo City, we connected to my own hospital, Hokuto Cardiovascular Hospital, and a hospital in Muroran (another large city in Hokkaido) via fiber-optic link and showed a PCI procedure*2 to doctors involved in interventional cardiology and heart surgery in Hokkaido. The quality of the images produced by the Safire system raised quite a stir.

In the future, by holding similar demonstrations connecting Sapporo to other major cities in Hokkaido via fiber optics, I hope to foster the creation of a network stretching all over Hokkaido and gradually establish a system for the regional coordination of medical treatment.

*1 **Drug-eluting stent :** *Restenosis may occur in a coronary artery even if a stent is used. As an improvement on the conventional stent, a "drug-eluting stent", namely, a stent that has been coated with a drug that prevents restenosis, is used.*

*2 **PCI (Percutaneous Coronary Intervention) procedure :** *General term that refers to any procedure used to perform coronary revascularization with a catheter by expanding a blood vessel at a point where stenosis has occurred due to ischemic heart disease, such as angina or myocardial infarction.*

Even Smaller, Even Faster An Eye That Watches for Changes in Body Functions

Whole-body PET System

The PET (Positron Emission Tomography) system diagnoses cancer and other diseases by identifying changes in body functions. Shimadzu is currently the only manufacturer of clinical PET systems in Japan. The new PET-Eminence-G system, released in Japan this spring, offers even higher resolution and will create new possibilities in PET examinations.


Eminence-G system

Identifying Disease from Body Functions

The PET (FDG-PET) examination has become the subject of increasing expectations as a means of further investigation when the results of a urine or blood test suggest the possibility of cancer. While MRI and CT scans are used mainly to investigate forms within the body, PET scans are used to observe functional and physiological processes, such as the consumption of glucose.

In examinations for cancer, a radioactive isotope and a constituent similar to glucose are combined to produce a drug called ^{18}F-FDG and this is injected into the patient's body. Taking PET scans once the FDG has flowed all over the body provides images that make it possible to observe the way that, for example, the FDG gathers around malignant tumors. The whole body can be screened in just one examination and so there is little invasiveness on the patient, and even in the early stages of cancer it may be possible to find tumors in places other than those already known.

In the U.S., this treatment has become so widespread that many medical practitioners observe a policy of "PET first" when faced with a suspected tumor. Following the decision to extend public insurance cover to ^{18}F-FDG in April 2002, it is hoped that the treatment will become equally widespread in Japan.

Anticipating an Expanded Range of Application

Shimadzu has been performing R&D in PET technology for over 20 years and is the only manufacturer of clinical PET systems in Japan. Shimadzu possesses a high level of technology in this field, with the capacity to achieve quantitativity and short acquisition times. The new model due for release this spring offers an even higher level of resolution than previous models and, as a whole-body clinical PET system, it currently offers the highest spatial resolution in the world. The potential of this system to discover early-stage cancer that would, until now, have gone undetected is keenly anticipated.

The application of PET is not restricted to examinations for cancer. The same fundamental technique can be used to perform examinations for heart or brain disease by injecting, for example, ^{15}O-water or ^{13}N-ammonia. The whole body can be examined in one screening with minimal burden on the patient. With increased resolution, the capabilities of PET seem set to expand even further.

Shimadzu's new PET system Eminence-G was introduced to the Japanese market this spring at the International Technical Exhibition of Medical Imaging and the Japan Radiology Congress 2004 held in Yokohama.

In order to truly satisfy our customers

Quality customer support the value of our products

The latest technology or excellent products do not always meet the needs of customers without adequate customer support. In addition to providing the latest quality products, Shimadzu offers complete customer satisfaction by working with individual customers to meet their specific needs. In this article, Mr. Shigehiko Hattori, President & CEO of Shimadzu Corporation, tells how Shimadzu does it.

Enhance the group's ability to satisfy customers

One year has passed since I became president last June.

Shimadzu Group achieved most of the goals for the second year in its three-year medium-term management plan (FY2002 to 2004).

This is the last fiscal year of the medium-term management plan. We are working hard to build a firm foundation to achieve our sales goal of ¥230 billion.

Shimadzu Group consists of companies with the sprit of self-sustainment. Each company is specialized in a unique field with the technology, products, know-how, and personnel particular to that area. After studying our group's strategies, we decided to restructure management because a lot more can be accomplished by streamlining the group's resources.

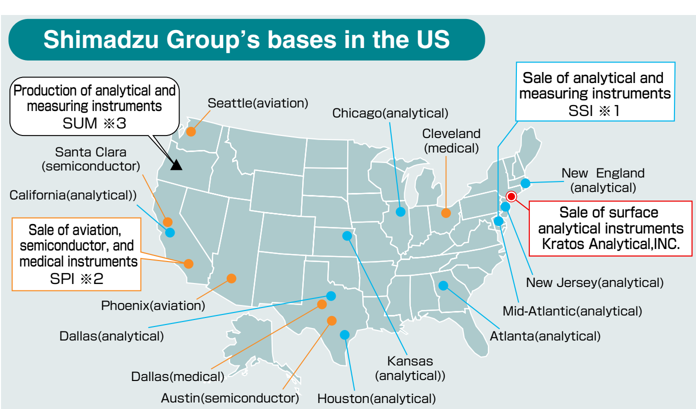
We are working towards a system that can attain even higher levels of customer satisfaction by sharing information within the group and improving each company's ability to deal with customers and develop products. We are also strengthening the training programs for sales and service personnel in our overseas bases.

Strengthening bases in the US and China

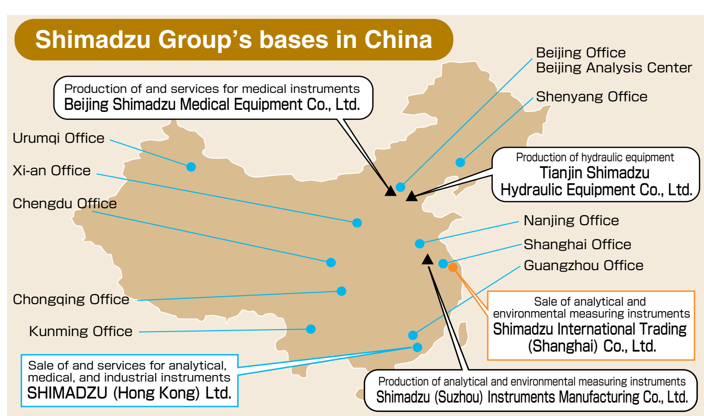
In reviewing group management, we are prioritizing the demands of customers overseas.

We plan to strengthen and expand our customer support systems in the US, the world's largest market, and China with its rapidly growing economy.

Because of cutting-edge research in the biotechnology, information technology, and nano-technology fields in the US, there is a high demand for our main products, analytical and measuring instruments in the US market. We are increasing significantly the number of customer support personnel including service persons. We are also enhancing the level and number of our salespersons in order to expand our business in the US. We are striving to address customers' needs more accurately, respond to them quicker, and improve our customer support systems so that customers become more aware of the Shimadzu brand.



●—SSI sales bases ※1 SHIMADZU SCIENTIFIC INSTRUMENTS, INC.
●—SPI sales bases ※2 SHIMADZU PRECISION INSTRUMENTS, INC.
(Medical systems:SHIMADZU MEDICAL SYSTEMS DIV.)
▲—Production base ※3 SHIMADZU U.S.A. MANUFACTURING, INC.



●—Sale bases of SHIMADZU (Hong Kong) Ltd.
▲—Production bases

increases

Shigehiko Hattori,

President & CEO of Shimadzu Corporation

China is another important part of our overseas strategy. The Chinese economy rapidly grew after joining WTO in December 2001. Because Chinese companies are trying to improve product quality, demands for analytical and measuring instruments are rapidly increasing. In addition to product quality improvement, efforts to achieve an international-level in environmental protection and medical care are being made. As a result, more sales in these areas are expected.

The relationship between Shimadzu and China started at the First Beijing, Shanghai, Japan Trade Show held in 1956. We opened a business base there in 1979. Because of our long-standing relationship, a number of Chinese institutions have installed Shimadzu products. We have established business bases in both inland and coastal areas. We plan to expand our distributors network based on our ten sales bases in China in order to satisfy customers' needs.

Meeting the demand to see things once not visible

We have developed world-class products that are useful in various fields. Our analytical and measuring instruments became well-known after Shimadzu's Mr. Tanaka received a Nobel Prize in 2002. In the field of medical instrumentation, last year's newly-released flat panel detector, a revolution in x-ray technology, has been met with accolades in Japan and foreign countries for its high performance.

Shimadzu has worked hard to meet the demands of researchers and medical professionals since its foundation. To see things once not visible and to measure things once not measurable has long been the dream of people in these fields. With a highly qualified and innovative product development staff, Shimadzu works towards making those dreams a reality in its quest to produce quality products.

Based on this basic belief, Shimadzu continues to work towards satisfying our customers by reforming our organization and increasing staff consciousness and motivation. Through this process, we continue a tradition of easy-to-use applications and quality support systems.

We are doing our best to become even better.

Total Solutions for Meeting European Environmental Regulations

The key to green procurement is being able to perform inspections accurately and quickly

The European Union has issued two note-worthy environmental directives last year. These directives seek to have the companies that manufacture electronic products be socially responsible for protecting the environment. With a corporate philosophy of realizing the wishes for the “Well-being of Mankind and the Earth”, Shimadzu is moving rapidly to have their own products fulfill these directives. Furthermore, Shimadzu is strengthening its ability to help customers meet the E.U. standards through its analytical and measuring instruments.

The E.U. Environmental Directives

With industrial growth and concentrated populations, Europe is facing serious problems with environmental pollution (such as the Chernobyl accident, Rhine River pollution, acid rain problem, and the mounting industrial waste from automotive and electronic industries). In response, the E.U. has issued two environmental directives in February 2003: the Directive on Waste Electrical and Electronic Equipment (WEEE) and the Directive on the Restriction of the Use of Certain Hazardous Substances in Electrical and Electronic Equipment (RoHS). All the member countries must achieve the results specified in these directives, but each member country is responsible for choosing by what methods and procedures. The purpose of WEEE is to prevent and reduce the waste of electronic and electrical equipment through recycling, reuse and recovery. WEEE applies to almost all electric and electronic devices.

The RoHS directive prohibits the use of six substances that are considered highly hazardous (mercury, cadmium, lead, hexavalent chromium, and brominated flame retardants polybrominated biphenyl (PBB) and polybrominated diphenyl ether (PBDE). These substances are very toxic, so they have raised concerns regarding soil and water pollution and their effect on living organisms.

WEEE requires that each member country have domestic laws in place by August 13, 2004, and have manufacturers take responsibility for their waste from August 8, 2005 by implementing such measures as applying symbol markings (see figure) to applicable products. RoHS also requires that each member country have domestic laws in place by August 13, 2004, and prohibits the use of the six hazardous substances in electrical and electronic equipment from July 2006. Sales of products containing any of these six substances will be prohibited in the E.U.

Japanese Companies Respond to E.U. Requirements

Japanese companies that export products to any member country of the E.U. are under pressure to quickly comply.

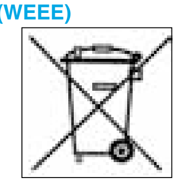
Final assembly manufacturers are asking their contract suppliers to prepare for the RoHS directive and are working to establish green procurement systems that comply with the RoHS directive. Furthermore, they have the urgent task of setting up inspection systems in order to eliminate the hazardous substances from the parts or materials they purchase.

The effects of these directives are not limited only to European regions. China and Korea are moving toward establishing regulations that consider these directives. In the United States, California has already passed a recycling law modeled after the WEEE and RoHS directives. In addition, the number of member states included in the E.U. itself, which was responsible for establishing these direc-

■Directive on Waste Electrical and Electronic Equipment (WEEE)
—— Effective from February 13, 2003

Purpose

- *The prevention of waste electrical and electronic equipment*
- *The reuse, recycling and other forms of recovery of such wastes so as to reduce the disposal of waste*



Symbol marking to be applied to products subject to WEEE

Scope of Products

1. *Large household appliances: Refrigerators, washing machines, microwaves, air conditioners, etc.*
2. *Small household appliances: Vacuum cleaners, irons, hair dryers, clocks, etc.*
3. *IT and telecommunications equipment: Personal computers, telephones, cellular telephones, etc.*
4. *Consumer equipment: Radio sets, television sets, musical instruments, etc.*
5. *Lighting equipment: Luminaires for fluorescent lamps with the exception of luminaires in households, etc.*
6. *Electrical and electronic tools: Lathes, welding tools, spraying tools, etc. (not including large stationary industrial tools)*
7. *Toys: Electric trains, car racing sets, video games, etc.*
8. *Medical devices: Radiotherapy equipment, cardiology equipment, analyzers, monitors, etc.*
9. *Monitoring and control instruments: Smoke detectors, thermostats, industrial monitoring and control instruments, etc.*
10. *Automatic dispensers*

■Directive on the Restriction of the Use of Certain Hazardous Substances in Electrical and Electronic Equipment (RoHS) —— Effective from February 13, 2003

Purpose

- *Coordinate the laws of the member states on the restrictions of the use of hazardous substances in electrical and electronic equipment.*
- *Contribute to the protection of human health and the environmentally sound recovery and disposal of waste electrical and electronic equipment.*

Note: This directive will ensure that from 1 July 2006, new electrical equipment does not contain heavy metals mercury, cadmium, lead, and hexavalent chromium, or brominated flame retardants polybrominated biphenyls (PBB) or polybrominated diphenyl ethers (PBDE).

Scope of Products *WEEE product categories 1, 2, 3, 4, 5, 6, 7 and 10, plus electric light bulbs and luminaires in households*

■Directive on End-of-Life Vehicles (ELV) —— Enforced on July 1, 2003

Purpose *The reuse, recycling and other forms of recovery of end-of-life vehicles and their components so as to reduce the disposal of waste*

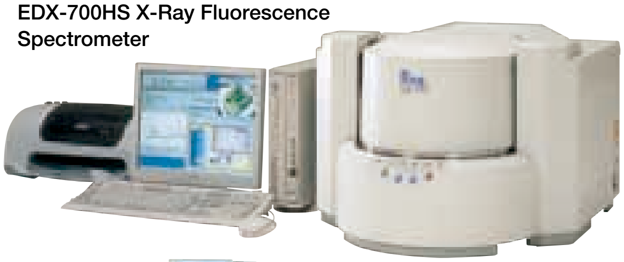
Prohibited Substances *The use of lead, mercury, cadmium, and hexavalent chromium is prohibited from 1 July 2003.*

tives, increased from 15 to 25 in May 2004. The E.U. is predicted to grow even more over the next ten years. Therefore, the E.U. will have an even greater influence on the environmental policy of individual countries throughout the world.

Shimadzu Provides Support to Meet Environmental Regulations

Based on technology cultivated over many years, Shimadzu has developed many environment-related products which are not only highly accurate and sensitive, but are also designed with ease-of-use in mind. For example, Shimadzu technology simplifies or eliminates pretreatment procedures and allows one machine to inspect simultaneously for multiple hazardous substances. Shimadzu can help customers establish a fast efficient inspection system focused on material inspection productivity. Shimadzu's strength is being able to provide customers a complete system of products to handle all the substances governed by the RoHS directive — total solutions tailored to the customer's specific product line. Shimadzu frequently conducts RoHS/ELV-related seminars throughout Japan which provide the latest information regarding the situation in Europe. Building accurate and efficient inspection systems is an extremely important issue. It is the foundation that must support global environmental policy. In order to realize the "Well-being of Mankind and the Earth", the expectations placed on Shimadzu analytical instruments are great.

Compatible with all substances regulated in RoHS and ELV directives
Shimadzu's Product Line of Analytical Instruments

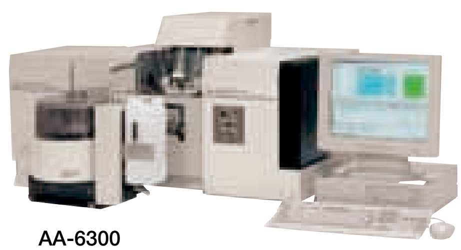


EDX-700HS X-Ray Fluorescence Spectrometer

ICPM-8500
Inductively Coupled Plasma Mass Spectrometer

UVmini-1240
Ultraviolet-Visible Spectrophotometer

ICPS-7510
Sequential Plasma Emission Spectrometer



AA-6300
Atomic Absorption Spectrophotometer

IRPrestige-21
Fourier Transform Infrared Spectrophotometer

Regulated Elements/Substances and the Corresponding Analytical Instruments

Hazardous metal/substance	Directive	Prescribed ELV and RoHS limits (See note 3.)	Recommended instrument for inspection	
			High-precision analysis	Screening
Cd,Pb,Hg	ELV and RoHS Directives	Cd:100 ppm Pb,Hg:1,000 ppm	Sequential Plasma Emission Spectrometer ICPS-7510/ICPS-8100 (0.1 ppm min.) Inductively Coupled Plasma Mass Spectrometer ICPM-8500 (0.0001 ppm min.) Atomic Absorption Spectrophotometer AA-6800/AA6300 (0.1 ppm min.)	Energy Dispersive X-ray Fluorescence Spectrometer EDX-700HS/ µEDX-1200 (5 ppm min.)
Hexavalent chromium	ELV and RoHS Directives	1,000 ppm	For analysis of total Chromium: Sequential Plasma Emission Spectrometer Inductively Coupled Plasma Mass spectrometer Atomic Absorption Spectrophotometer UV-VIS Spectrophotometer	For selective analysis of hexavalent chromium:(See note 2.) UVmini-1240 UV-VIS Spectrophotometer +Water-quality Measurement Program Pack (0.02 ppm min.)
				For analysis of total chromium: Energy Dispersive X-ray Fluorescence Spectrometer EDX-700HS/ µEDX-1200 (100 ppm min.)
Brominated flame retardants	RoHS Directive	1,000 ppm	Gas Chromatograph Mass Spectrometer GCMS-QP2010	For selective analysis: Fourier Transform Infrared Spectrophotometer IRPrestige-21/FTIR-8400S (5% min.)
				For analysis of total bromine: Energy Dispersive X-ray Fluorescence Spectrometer EDX-700HS/ µEDX-1200 (5 ppm min.)

Notes
1. The "ppm min." values are the minimum detection limits. The detection limits given for ICP and AA instruments represent the values obtained when 1g of the sample is dissolved in 100 mL of solvent.
2. Because boiling water,for example,is used for extraction in the pretreatment stage, hexavalent chromium is extracted from the surface layer only. Not all the hexavalent chromium is extracted.
3. The RoSH limits given in the table are tentative values that were still subject to discussion at the end of November 2003. They had not been officially recognized at this time.

Professor Yoshikazu Nakayama

Professor at Osaka Prefecture University Graduate School of Engineering, special professorship at Osaka University Graduate School of Engineering, Frontier Research Center, and Doctor of Engineering. Graduated 1972 from Osaka Prefecture University College of Engineering. After working for Matsushita Electronic Industries Co., Ltd., moved to Osaka Prefecture University College of Engineering in 1979. Has held current position since 2000. Awarded the 2003 "Nano Probe Technology Award" from the Japan Society for the Promotion of Science.

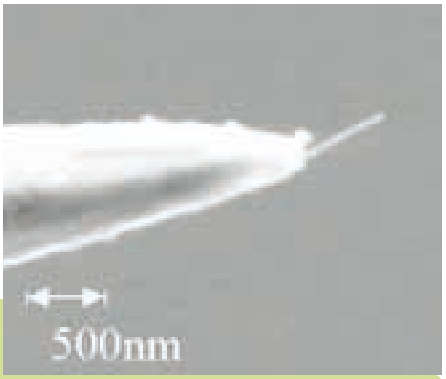
The Fruit of Collaboration between Academia and Industry

An "Ultra-Small Electron Microscope" Born from Carbon Nanotubes

The relationship between industry and academia is becoming more active in recent years. Shimadzu has long held a close relationship with the academic community through development of various products for researchers and is continuing its joint development programs enthusiastically. One of those joint development projects has born fruit with great potential. A single nanotube, developed in partnership with Professor Yoshikazu Nakayama of Osaka Prefecture University, has given birth to technology for making the key component of an electron microscope.

The World of Billionths of a Meter

Consider vinyl records making a noticeable comeback recently among young people. A record player produces sound by rubbing a stylus made of diamond or ruby along a bumpy groove cut into a polyvinyl chloride disk. A coil converts the resulting vibration into an electric signal, which the amplifier amplifies. The grooves on a LP record are about 0.05 millimeters wide and the needle thickness is about 0.026 millimeters, or 26 microns. In contrast, the world of carbon nanotubes is at a scale one thousand times smaller.



A carbon nanotube attached to the tip of a tungsten needle

In the U.S., a music critic once became a topic of conversation in the 1980's by identifying song titles from looking only at the record grooves. However, the nano-world cannot be seen with the naked eye. At the nano-level, one is able to see DNA, molecules and even individual atoms. Now carbon nanotubes are trying to provide a clear view into that smallest of worlds.

The Hardest and Most Flexible of Materials

Carbon nanotubes are a mesh of carbon atoms connected together like a beehive that forms a tube. The tube is a mere one to a dozen or more nanometers in diameter. Claimed to be the lightest and strongest material on earth, a 0.3 millimeter thick tube would have the strength to lift an automobile weighing a ton. These amazing properties have attracted the attention of researchers and companies around the world.

Sumio Iijima discovered carbon nanotubes in 1991. He announced his discovery in the science magazine "Nature." Mr. Iijima currently heads the Research Center for Advanced Carbon Materials at the National Institute of Advanced Industrial Science and Technology. Carbon nanotubes have caused quite a reaction. "To be honest, I thought this could be a winner," recalls Yoshikazu Nakayama, of Osaka Prefecture University, Graduate School of Engineering. At the time, Prof. Nakayama was studying in the United

States. As soon as he saw the news he immediately realized the potential and began research. That research resulted in the probe used in scanning probe microscopes (SPMs).

That probe consists of a plate spring, called a cantilever, that is fixed on one end and has a carbon nanotube attached to the free end. By drawing the probe across the sample surface, the contour of the sample surface can be measured. A typical application of the SPM technology is the atomic force microscope (AFM), which detects the atomic forces (the attractive forces generated between atoms) acting between the probe tip atoms and the sample atoms. The obtained data is processed into a three dimensional image by a computer.

"Carbon nanotubes have five to ten times the hardness of steel, yet are very flexible and won't break easily even if they are bent over. That's why I thought they were worth pursuing," explains Prof. Nakayama. Two years later, a scanning probe microscope containing a carbon nanotube was sent out into the world via a joint venture with a commercial company. Prof. Nakayama has also developed other products that employ carbon nanotubes, such as tweezers. "They're the perfect size for gripping DNA. I'd be happy if they are used as a set," Prof. Nakayama stated laughingly.

Shigeki Hayashi
Senior Researcher at Shimadzu Corporation's Technology Research Laboratory

Potential Electron Source

Carbon nanotubes also have another property that is worth pointing out. That is their high electrical current capacity, said to be more than ten times greater than copper, and their high aspect ratio. When a high voltage is applied to a carbon nanotube, an electric field builds up at its tip. Based on this fact, electrons can be discharged from a very narrow range on its tip.

Carbon nanotube development is a cutting-edge field attracting considerable attention from around the world.

Shimadzu is working on applying this property to emit electrons or x-ray radiation for next-generation electron microscopes.

"It would allow us to easily focus a microscope, so in the future perhaps we can make electron microscopes the size of a magnifying glass." That's how Shigeki Hayashi, senior researcher at Shimadzu's Technology Research Laboratory promotes the idea. "In order to make this electron microscope a reality, we must first attach a carbon nanotube to the tip of a tungsten needle that has a radius of only 100 nanometers and to do that Prof. Nakayama's help is essential."

That is how Shimadzu began researching the use of carbon nanotubes as micro field electron emitters. The results were extremely promising. Compared to previous electron emitters, electrons discharged from the newly developed emitter fell within a range that was about one tenth as broad. "That means we can increase resolution that much more and increase accuracy. Once we obtain stable results then we should be able to make electron microscopes that are dramatically smaller than current systems," Mr. Hayashi stated.

Furthermore, standard electron emitters require use in an ultrahigh vacuum environment to prevent reactions with impurities in the air. However, carbon nanotubes do not react easily with impurities, so they are able to operate in vacuum levels that are one hundredth lower than the vacuum level required for standard emitters. "Electron microscopes can be used without installing an expensive vacuum pump system. That should increase their usage to a new level," predicts Hayashi.

Sending Them Out into the World As Soon As Possible

Shimadzu is already looking ahead and considering applying the technology to x-ray emission. The idea is to look inside objects using a nano-sized x-ray beam. For example, it would make it possible to check the internal circuits inside finished semiconductors.

Prof. Nakayama stated, "It's fun working with Shimadzu. The researchers are passionate and always pursuing their dreams. This is the result of taking full advantage of the properties of carbon nanotube, like its application in SPM probes. I want to send them out into the world as soon as possible." This new fruit born of a collaboration between industry and academia is about to be sent into the world soon.

Interview

Keeping "Eyes" on the

Human bodies are made of proteins. Grasping their form should give us an understanding of the structure of our bodies
The mass spectrometer is an instrument that lets us see how proteins work inside the body. Shimadzu Corporation pro-
Shimadzu developed a new method that dramatically simplifies protein analysis.
The discovery of idiosyncratic proteins during disease is expected to revolutionize drug development and medical treat-

Proteomics — a Business of the Future

Dr. Osamu Nishimura is a pharmaceutical specialist who participated in the development of many drugs at Takeda Chemical Industries, Ltd. He has a unique background among the mechanical, electrical and applied physics specialists at Shimadzu Corporation.

Osamu Nishimura
Senior Corporate Officer, Shimadzu Corporation
Deputy General Manager, Analytical & Measuring Instruments Division
General Manager, Life Science Laboratory
Manager, Proteome Analysis Center

Joined Takeda Chemical Industries, Ltd. after obtaining a master's degree from Graduate School of Pharmaceutical Sciences, Kyoto University.
Successively became General Manager of the Takeda Biotechnology Research Laboratory and Pharmaceutical Discovery Research Division. Joined Shimadzu Corporation in 2001. Doctorate in Pharmacy
Visiting Professor at Osaka University

Nishimura moved to Shimadzu in July 2001. Former Takeda president Masahiko Fujino (currently Corporate Advisor) had been Nishimura's immediate superior from the time he entered the company. There was a reason why Fujino let his favorite disciple, who held the important position of General Manager of the Pharmaceutical Discovery Research Division, go to Shimadzu.

As the analysis of the human genome progressed, the focus of pharmaceutical development shifted to genome-based drug discovery. This is a method to develop the most effective drugs to combat a disease through investigations into the idiosyncratic actions of genes during the disease. Takeda was close to completing a system for research on drug discovery based on genomic information.

However, Nishimura, as a scientist, wasn't entirely satisfied. "Genes are the blueprints for proteins, and the body is essentially composed of proteins. These proteins change ceaselessly moment by moment due to the effects of hormones, water, and other proteins in the body. I came to think that we couldn't make effective drugs without investigating the actions of such proteins."

The future lifeline of pharmaceutical development is simply the careful examination and study of protein actions. Fujino certainly believed this as well. So they sought a setting where they could intensively conduct their investigations into proteins.

Stable Isotope Identification Kit for Proteome Expression Analysis

At the time, Shimadzu was establishing itself in the promising business field of protein analysis, centered on its "soft laser desorption/ ionization methods."

Shimadzu Corporation had many excellent mechanical, electrical and applied physics specialists, but it lacked biologists and chemists. Top management realized that people with a comprehensive knowledge across the field were essential to seriously tackle the life sciences, and began headhunting. Thus Nishimura was singled out as a person who could effectively bridge the expertise of the two companies.

"After being appointed, my first task was to establish the Life Science Laboratory in Shimadzu. Due to the lack of experts in biology and chemistry at the company, first I had to gather personnel from a variety of places," recalls Nishimura.

Tagging Amino Acids

The Life Science Laboratory, which initially started with just ten staff members, has achieved a remarkable result. It developed a new analytical method to discover proteins in blood or tissue that are generated during an illness.

Trace amounts of proteins not normally found are generated when an illness occurs, creating a different protein balance from the healthy state. The compilation of data on diseased and healthy states will possibly permit the accurate diagnosis of the name and severity of the illness in the future simply by investigating the amounts of protein present.

Proteome analysis, as a field of life science, is currently generating the most interest around the world. This analysis method might form the launch pad for developing medicines based on protein information.

Nishimura is the central figure in this development.

Nishimura focused on the amino acid tryptophan for a method of efficient proteome analysis. Tryptophan is an amino acid that plays an important role in proteins. It occurs in almost all of the tens of thousands of proteins but the amount contained in one individual protein is among the lowest of all amino acids.

Nishimura's idea was to "tag" tryptophan. He ground up cells taken from the body and added tags to the tryptophan in the sample. He then used a mass spectrometer to list the proteins in the sample sequentially from lightest to heaviest.

The Eye That Studies the Body

This method was applied to the cells of healthy and diseased subjects. The tryptophan of

Path to Proteomics

and the overall mechanisms of life, including memories and thoughts.
duces the premier mass spectrometers and protein analysis methods. In July last year,

ments. Osamu Nishimura and Koichi Tanaka were the key to this development.

Koichi Tanaka
Shimadzu Fellow
Director, Koichi Tanaka Mass Spectrometry Research Laboratory,Shimadzu Corporation

Joined Shimadzu in 1983 after graduation from Tohoku University.
Awarded the Nobel Prize in Chemistry 2002 for the development of soft desorption ionization methods for mass spectrometric analyses of biological macromolecules.
Visiting Professor at Tohoku University, Kyoto University, Tsukuba University, and Ehime University

healthy people was tagged, for example, "green", and the tryptophan of diseased people was tagged "red". They were then mixed together. This resulted in a matching number of "green" and "red" tags for most proteins, but some non-matching tags were also discovered. These proteins change in quantity idiosyncratically during an illness.

A database of diseases and the idiosyncratic increase or reduction in proteins correlating to each disease can be created from data accumulated by repeatedly applying this method. This should allow disease identification from a simple blood test.

The tags used in practice are carbon isotopes. Tags incorporating the carbon isotopes ^{12}C and ^{13}C, which have different masses, were attached to the tryptophan.

Nishimura's extensive knowledge of biochemistry was a major factor in focusing on tryptophan. Although significant research is being conducted around the world, few successes have been achieved so far. Most of these attempts use the amino acid cysteine as the target.

Nishimura explains, "After long years of studying the human body, I had a gut feeling that we should choose tryptophan to investigate the amounts of protein."

"The reason I am so pleased to have come to Shimadzu is that they produce world-class mass spectrometers and I had access to the next-generation prototypes. Without such high sensitivity, I may never have thought of measuring such small mass differences."

The meeting of the "eye" with which Nishimura studies the human body and the "eye" of the mass spectrometer that views proteins has achieved significant results. They watch over the bright path of proteomics.

A More Sensitive and Accurate View of Proteins

In 2002, Koichi Tanaka was awarded the Nobel Prize in Chemistry for the soft Laser desorption/ionization method that he invented in 1985. The mass spectrometer based on this method has been significantly improved since the 1980s, particularly in terms of enhanced sensitivity and accuracy. Where instruments at that time could only detect the weight of 600 trillion protein molecules, today's instruments are over a million times more sensitive and are able to detect just a few hundred million molecules.

Similarly, the accuracy has improved from the initial ±0.1% error to just 0.001% in the latest AXIMA Series instruments. These improvements now offer accurate, sensitive and rapid mass spectrometry. The success of the tryptophan method described before is attributed entirely to the performance of the AXIMA Series.

Tanaka states that he used the AXIMA Series to help confirm the ideas that Nishimura had been considering over a long period.

Protein analysis using these instruments has formed the basis of realizing the dream of disease diagnosis.

"The next step was to determine what type of system we could create using this method and the proper reagents to achieve good proteome analysis," stated Tanaka.

Bedside Protein Analysis

Tanaka, who is once again able to work as a researcher and scientist, looked back over the research for which he was awarded the Nobel Prize: "At that time, I was concentrating on doing research every day. Even now, my days revolve around solid research. I achieved my dreams through this accumulated bulk of work. The most important thing is to maintain a balance between pursuing dreams and achieving results through steady fundamental and applied research."

MALDI-Quadrupole Ion Trap-TOF Mass Spectrometer AXIMA-QIT

One of those dreams is research into sugar chains. As the name suggests, these are substances formed from sugars linking together like a chain. They play an extremely important role in a various protein functions. An estimated 30% of proteins function due to bonded sugar chains. Consequently, research into proteins alone cannot provide greater understanding of life or human molecular mechanisms. Research into the sugar chains attached to the surfaces of proteins is important in understanding the phenomenon of life.

The analysis of sugar chains is extremely difficult and the existence of sugar chains was conventionally ignored when studying proteins. This situation is now changing, thanks to the AXIMA Series.

"Japan is the world leader in sugar-chain research. To further promote this research, I hope to aid other researchers by developing an analysis method for sugar chains," explains Tanaka.

Another of his dreams is to use proteins to screen for disease. The ability to rapidly detect disease through protein analysis of blood samples would dramatically improve public health screening initiatives. The sensitivity, accuracy, and compact nature of the analytical instruments are the key to such research and development.

Tanaka added, "Protein analysis by mass spectrometry is extremely effective for screenings to determine the presence of disease. Abnormalities can be detected in the tiny amounts of protein present in minute samples of blood. I hope that protein analysis will become one means of health screening in the future."

Work in the current topic, development of reagents for proteome analysis, should be one step along this path. In the near future, protein analysis may be as simple as blood pressure measurements are today.

Who is beyond the Ocean

Shimadzu Research Laboratory (Europe) Ltd. (SRL)

Improving the Quality of Research through Cooperation with Outside Researchers

Managing Director: Sumio Kumashiro

Location

Location : Manchester, U.K.
Date of foundation : April 1997
Capital : £300,000
Number of employees : 25
Research areas : Surface analysis, mass spectrometry, optical technology, collection and provision of technical information

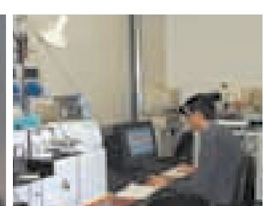
This research laboratory was established in April 1997 as a wholly owned subsidiary of Shimadzu Corporation. It later became a subsidiary of Shimadzu Europe Ltd. (SEL), which is a regional holding company of Shimadzu in Europe. Since then we have been primarily engaged in work commissioned by Shimadzu headquarters and have functioned as a European base for core technology R&D as well as collecting and providing technical information for the Shimadzu Group. The U.K. was selected as our base of operations because of its academic environment, which has greatly contributed to technological development in the fields of mass spectrometry and surface analysis. The U.K. also has a long tradition and history of fostering basic research. Another reason that SRL was established in Manchester, U.K., was to share premises and facilities with a closely affiliated firm in the Shimadzu group, KRATOS, who produce surface analysis equipment and MALDI- TOF mass spectrometers.

Our establishment as a research laboratory in 1997 was accompanied by assignments from Shimadzu Corporation to push forward the development of basic technology for mass spectrometers and scanning electron microscopes (SEM). These projects lasted up to five years. One result of our research is the MALDI-Quadrupole Ion Trap-TOF Mass Spectrometer AXIMA-QIT, which has been released as a product by KRATOS.

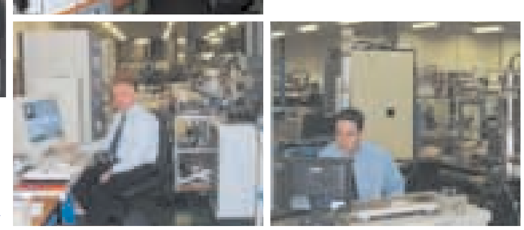
Since then, while centering on hardware development for mass spectrometers and SEMs, we have gradually expanded our research areas to include bio and nanotechnology. In the field of mass spectrometry, we have started basic research on new types of ion-trap technology, algorithms for determining the amino-acid sequences of proteins, and reagents for the quantitative and comparative analysis of proteins. In the field of SEMs, we are pushing forward with research on algorithms for processing spectral imaging data, ultrasensitive electron-energy analyzers, ultra-low acceleration compact SEMs, and aberration-corrected electronic optical systems. These research projects are just starting to bear fruit. How to make effective use of research results is the subject of continuing debate, but one option being considered is the transfer of technology to either the Technology Research Laboratory or the Koichi Tanaka Mass Spectrometry Research Laboratory at Shimadzu Corp. so that the technology may be further evaluated for potential applications and its feasibility for commercialization assessed.

The SRL is a relatively small-scale operation and we place great importance on cooperation with researchers outside the company. We will continue striving to improve the quality of research by strengthening our relationships with other research organizations. We are also accumulating technical know-how in areas such as design technology for electron/ion-beam optical systems, algorithms for processing data and controlling equipment, and the design of high-precision power supplies. All of us here will continue to make every effort to ensure that these research activities lead to bigger growth of the whole Shimadzu Group.

▲ *Employees at a meeting*



◀ *R&D for mass spectrometers*



Development of SEMs and related technology ▶

Exhibition

ITEM2004 in Yokohama

Innovations for Advanced Imaging-Advancement of Key Technology

The International Technical Exhibition of Medical Imaging 2004 (ITEM2004) is Japan's largest medical imaging system exhibition. This year the exhibition was held from April 8th to 10th at the Pacifico Yokohama Exhibition Hall (Yokohama, Japan) together with the Japan Radiology Congress (JRC).

Shimadzu Corporation was an anchor exhibitor with one of the largest booths. With the theme of "Innovations for Advanced Imaging – Advancement of Key Technology," Shimadzu exhibited digital X-ray systems equipped with a new-generation direct-conversion flat-panel detector (FPD) and a new PET system. A record number of visitors visited the Shimadzu booth and the exhibition was a success.

The Cardiac & Vascular Imaging System "DIGITEX Safire" with direct-conversion FPD (9˝x9˝), released last October in Japan, created waves because of its outstanding image quality. The booth was filled with interested visitors and interventional radiologists keenly listened to explanations about the system. Many customers and other vendors visited the booth to learn about the large-area FPD (17˝x17˝) that is scheduled to be released soon. The Shimadzu booth was one of the most popular at the exhibition, reaffirming Shimadzu's strong presence and outstanding reputation as an FPD manufacturer.

There were many international visitors, some of which came with the specific purpose of asking Shimadzu's top management to release FPD-equipped systems overseas as soon as possible.

PITTCON2004 in Chicago

Shimadzu Introduces its Latest Technology to the World

PITTCON2004 was held in Chicago, Illinois from March 7th to 12th. This year there were about 25,000 visitors, a ten percent increase from last year's total (22,628). One reason for the increase was that the event was held in the North after being held in the South for several consecutive years. This was a very special PITTCON for Shimadzu. On the 8th, Shimadzu's Fellow Koichi Tanaka and Prof. Kurt Wüthrich of Switzerland, 2002 Nobel Prize laureate in chemistry, gave special lectures. Mr. Tanaka's lecture was titled "The Origin and the Future of Macromolecule Ionization by Laser Irradiation." Presented in the main lecture hall, the lecture was well received by many visitors. Shimadzu's Chairman Hidetoshi Yajima also paid a formal visit to the event as chairperson of the Japan Analytical Instruments Manufacturers Association (JAIMA) to discuss strengthening the cooperative relationship between the analytical instrument industries of the United States and Japan. In the exhibition held from March 8th to 11th, Shimadzu exhibited many new products such as the state-of-the-art spectrophotometer Solidspec-3700; Accuspot, a microfractionation spotter for MALDI-TOF/MS used in life science; and CHIP-1000 Chemical Printer for sample preparation in proteomics analysis. Shimadzu's new products impressed visitors with their excellence. "Laboratory Informatics" was the key topic of this year's exhibition, which epitomized the ongoing evolution of software in the analytical instrument industry in the era of information technology.

New Products

High-resolution Images Support Cardiac Examination and Treatment

X-ray Cardiac & Vascular System Featuring Direct-conversion FPD

Shimadzu has launched the DIGITEX Safire Cardiac & Vascular System featuring a direct-conversion flat panel detector (FPD) (an extremely high-sensitivity and high-resolution X-ray sensor) mounted to the C-arm. The X-ray cardiac and vascular system is a high-tech medical instrument that supports cardiac diagnosis and treatment. It comprises a C-arm equipped with an X-ray tube and an FPD, a table, an image-processor, and image-display monitors. There are two versions available: the HC model with ceiling-suspended C-arm and HF model with floor-mounted C-arm. (See article on pages 6 - 9 of this issue.)

▲DIGITEX Safire HF

▲DIGITEX Safire HC

Quick, Positive Positioning Supports Surgery

OPESCOPE ACTIVO Surgical Mobile C-arm Imaging System

Shimadzu has launched the OPESCOPE ACTIVO Surgical Mobile C-arm Imaging System. To maintain cleanliness and ensure easy positioning, no cables protrude from the C-arm that handles X-ray irradiation. This state-of-the-art design ensures sterility and caters for smooth and efficient surgical operation. The fully balanced positioning system ensures quick and accurate C-arm positioning operations. The high-capacity X-ray tube permits continuous fluoroscopy over extended periods. Users can store up to eight fluoroscopic images as standard. Pulsed fluoroscopy and a compensation filter reduce total X-ray dose without compromising image quality.

New Handle Design and Illumination Functions Enhance Workflow

X-ray Tube Support and High Frequency Inverter Generator

Shimadzu has launched a ceiling-suspended X-ray tube support and high frequency inverter generator to improve workflow in general radiography rooms and contribute to increased productivity. The new rounded handle shape simplifies positioning at all angles, including the complex angles required for radiography in orthopedic cases. The handle significantly enhances positioning operability. This equipment provides a powerful tool for X-ray radiography in not only normal examinations, but also in emergency situations where the patient cannot be moved.

▲CH-200M X-ray Tube Support and UD150B-40/L-40 Generator

Non-destructive Testing of Large Specimens for Electrical/Optical Applications

SolidSpec-3700/3700DUV UV-VIS Spectrophotometer

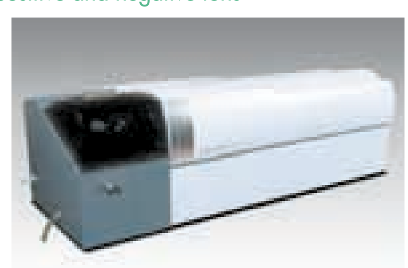
Shimadzu has launched the SolidSpec-3700 (standard model) and 3700DUV (deep-UV model) UV-VIS spectrophotometers best suited for the testing of electrical and optical components. They permit measurements of spectra across a wide wavelength range from deep UV to near IR, by switching between three detectors. They also have a large sample compartment to analyze large specimens without cutting.

The SolidSpec-3700 can measure highly accurate spectra across a wide wavelength range for full-surface measurements on 12-inch wafers, non-destructive testing of increasingly large FPD materials, and measurements for the evaluation and quality control of optical materials used in exposure equipment for semiconductor manufacturing.

LCMS-IT-TOF Liquid Chromatograph Mass Spectrometer

World First! Accurate MS^n mass measurements by rapid, simultaneous measurements of positive and negative ions

Shimadzu has launched the world's first liquid chromatograph mass spectrometer combining a high-performance liquid chromatograph that can separate a variety of chemical compounds, an ion trap (IT) mass spectrometer able to fragment molecules, and a time-of-flight (TOF) mass spectrometer permitting high-resolution and high-accuracy mass measurements. It takes full advantage of the features of the two mass spectrometers (IT and TOF) to achieve sensitive and accurate measurements of detailed molecular structures.



In addition to the easy-to-use, high-throughput MALDI-TOF mass spectrometer AXIMA Series, Shimadzu now offers easily automated LCMS-IT-TOF Liquid Chromatograph Mass Spectrometer that provides more diverse information. This powerful combination will contribute to reduced analysis times and higher reliability in life sciences and pharmaceuticals research.

High-throughput Proteome Analysis

AccuSpot LC Microfractionation Spotter for MALDI Plates

Shimadzu has launched the AccuSpot LC Microfractionation Spotter for MALDI plates. AccuSpot automatically spots eluates separated by HPLC onto target plates for MALDI-TOF mass spectrometers such as Shimadzu AXIMA Series. It enhances the work efficiency of MALDI-TOFMS analysis by automating sample spotting procedures.

AccuSpot allows Shimadzu to offer a total analysis system for all stages from separation by HPLC to analysis by MALDI-TOFMS.

To speed up the development of the life sciences, this product is sold in combination with 2D micro-HPLC, another effective tool for proteome analysis.

Micro-scale On-membrane Digestion for Protein Analysis

CHIP-1000 Chemical Printer

During pretreatment of protein samples for analysis by a MALDI-TOF mass spectrometer, proteins are separated by 2D electrophoresis and dispensed as spots (approx. 1 mm diameter) onto a membrane. The CHIP-1000 Chemical Printer delivers picoliter volumes of reagent to specific locations within the protein spot of interest.

Thanks to technologies for accurate positioning on the membrane and for dispensing minute samples (similar to the technology used for inkjet printers), the CHIP-1000 Chemical Printer is the first instrument in the world to allow microanalysis within protein spots. Shimadzu jointly developed the CHIP-1000 with Proteome Systems Ltd. (PSL), an Australian bio-venture.

New Reagents Launched for Protein Analysis by MS

Contributing to Protein Research for Medicine and Drug Discovery

Shimadzu has launched a Stable Isotope Labeling Kit for the quantitative comparison and analysis of protein expression by mass spectrometry. The reagent kit is ideal for the comprehensive and quantitative analysis of protein expression unique to specific diseases in biosamples, including blood, cells, or tissue. It is highly effective for the identification of diseases and the development of effective new drug for the treatment.

The reagents work on the tryptophan in the proteins, making the analysis results of mass spectra clear and simplifying analysis. Analysis costs can be reduced by combining the reagents in this kit with a simple concentration method.

(See article on pages 17 - 18 of this issue.)

Distortion-free Images even from Tilted Angles by Using Flat-panel Detector

SMX-1000 Digital Microfocus Industrial X-ray TV System

Shimadzu has launched the SMX-1000 Digital Microfocus X-ray TV System for use in industrial applications. It adopts a flat-panel detector (FPD) that detects X-ray images of the specimen as digital image data to ensure clear distortion-free images. The equipment displays a fluoroscopic image of a specimen by passing X-rays generated from an extremely small X-ray source through the specimen. This type of non-destructive test instrument is widely used in the electronics and other industries. Software for image processing and instrument control makes operation simple and easy.

Accurate Control and Measurement of Micro Displacements and Micro Test Forces Micro Strength Tester for Electronic Components

MST-I Micro Autograph

Shimadzu has launched the MST-I Micro Autograph to conduct accurate strength testing through the control and measurement of micro-range displacements (0.02 μm min.) and test forces (2 mN), targeting testing of electronic chip components. A servomotor and precision ballscrew apply loads to samples at 5-nanometer control resolution. Forces in the specimen are controlled and measured by a load cell, while deflections are controlled and measured by a linear scale. The optional TRAPEZIUM 2 data-processing software offers additional functions including ultra-high-speed sampling, voice navigation, network compatibility, and storing of various testing parameters.

Access to **your** success

SHIMADZU

2004.no.36

SHIMADZU CORPORATION

Executive Secretariat & Public Relations Department

TEL: +81-75-823-1145 FAX: +81-75-823-1361