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TNO Health Research



This brochure provides a description of TNO Health Research. This division, (in Dutch, TNO-Gezondheidsonderzoek), carries out most of the health-oriented research within TNO. TNO is the 'Netherlands Organization for Applied Scientific Research'. Apart from health research, TNO is also engaged in research in other areas, such as industrial technology, energy, the environment, nutrition and food, building and infrastructure, and defence. It is the task of TNO Health Research to contribute to the improvement of public health by doing applied strategic research. 'Applied' implies that it is application-oriented and 'strategic' indicates the necessity of the long-term continuation of this type of research.

The infrastructure in which TNO Health Research performs its tasks is mainly determined by the Dutch government, universities, allied institutes, sponsors and supporting agencies. The government departments concerned are mainly the Ministries of Welfare, Public Health and Culture; Education and Science; Social Affairs and Employment; Housing, Physical Planning and Environment and the Ministry of Defence. At universities, the Faculties of Medicine and University Hospitals are principally involved. Allied institutions are the National Institute for Public Health and Environmental Protection (RIVM), the Dutch Cancer Institute (NKI), the Netherlands Red Cross blood transfusion service (CLB) and the National Hospital Institute of The Netherlands (NZI).

Sponsors are found in trade and industry, in particular in the biopharmaceutical and chemical industries. Finally, TNO Health Research is subsidized by national organizations such as the Dutch Cancer Foundation (KWF), the Prevention Fund and the Heart Foundation as well as by international bodies such as the European Community (EC).

This brochure presents an overview of research activities of TNO Health Research within this framework. It is a comprehensive and dynamic programme, the result of a long history and based on the large amount of expert knowledge within the organization. The division is able to react adequately to developments in society, while maintaining its independent responsibility which guarantees both the quality and the continuity of its research.

We sincerely hope that the information in this brochure will increase your understanding of TNO Health Research and will facilitate your contact with us so that your signals, needs and wishes may be noted and we can take these into account when planning new research.

A handwritten signature in black ink, appearing to read 'W.F. Stevens', is written over a solid black horizontal line.

Dr W.F. Stevens
Director TNO Health Research

TNO Health Research

TNO Health Research is one of the seven divisions of TNO the Netherlands Organization for Applied Scientific Research. An overview of the research and development (R&D) facilities of TNO is presented on the inside cover of this brochure. Each division has its specific area of interest, viz. TNO Building and Construction Research, TNO Industrial Research, TNO Nutrition and Food Research, TNO Defence Research, TNO Environmental and Energy Research and TNO Policy Research. The Organization is administered by the TNO Board of Directors. TNO was established by a special Act of the Dutch Parliament in 1930. A revised 'TNO Act' became official in 1986. TNO has grown into an administratively independent, autonomous research organization with corporate status.

TNO Health Research is organized as illustrated on the inside cover. About 750 employees carry out their research activities at four institutes (two located at Leyden and two at Rijswijk), and at the TNO Radiological Protection Service in Arnhem and the Institute for Rehabilitation Research in Hoensbroek. The TNO Institute of Preventive Health Care (NIPG) and the new TNO Institute of Ageing and Vascular Research (IVVO) are located in Leyden. The institutes at Rijswijk are the TNO Medical Biological Laboratory (MBL) and the laboratory created by the fusion of the TNO Primate Center and the TNO Radiobiological Research Institute: the TNO Institute of Applied Radiobiology and Immunology (ITRI).

The primary task of TNO Health Research is to contribute to the improvement of public health and health care by performing applied strategic research concentrating on:

- gaining knowledge of the prevention and etiology of illnesses, aberrations and disabilities;
- developing methods and techniques for prevention and therapy;
- evaluating established and new methods and structures in health care, in particular concerning the quality of care and cost effectiveness.

The research activities of TNO Health Research focus on the support of health-policy development and implementation in those areas of health care that have been given priority by the government

and in which knowledge of applied medical, medical-technological and medical-social sciences plays an important role.

This type and range of work involves TNO Health Research in numerous connections with other branches of TNO and with many national and international organizations. The groups mainly concerned are: health-care authorities, industries, governments or organizations that make use of the know-how of TNO Health Research and its new developments in health care.

Many TNO Health Research staff members participate temporarily or permanently in external advisory bodies.

The division is supported at divisional level by a Programme Advisory Board and at institute level by Institute Advisory Boards. At several organizational levels, TNO Health Research is supported by experts from government, industry and other institutions of importance to TNO Health Research.

The major part of the research programme of TNO Health Research is commissioned by the Government. The Minister of Education and Science is responsible for the coordination of government policy regarding the TNO organization including TNO Health Research.

The main sources of revenue of TNO Health Research are a basic subsidy, special-purpose subsidies and contract R&D. The basic subsidy from the Department of Education and Science is intended to maintain high scientific standards and can be allocated by TNO Health Research itself. Special-purpose subsidies are at present granted by seven Dutch ministries on the basis of agreements between the ministries and TNO Health Research. Activities concerning these subsidies are evaluated annually.

TNO Health Research has close connections with the national and international academic world. These connections usually range from joint projects to combined institutes and other joint ventures. In addition, several experts of TNO Health Research occupy chairs at Dutch universities. In this way,

national and international know-how and research experience are used to the full.

Other research establishments, consumer organizations, specific branch associations, industries and companies plan and fund research programmes in collaboration with TNO Health Research.

Research within TNO Health Research is concentrated on the application of new findings in medical-biological and social sciences to clinical and preventive health care. Research on laboratory animals is important, particularly in cases where insufficient data are available to justify human research. In addition, TNO Health Research cooperates with medical schools and hospitals to carry out clinical research.

TNO Health Research participates in a wide area of health-care research. This is partly the result of historical developments: TNO Health Research

originated from separate institutes, committees and study groups, each with its own background and ethos. In attempting to formulate a coherent research programme, TNO Health Research has adjusted and improved its programme over the years.

TNO Health Research covers the following areas of interest:

1. Prevention and health care
2. Gerontology
3. Cardiovascular research
4. Medical Technology and Rehabilitation
5. Radiation and Health
6. Chronic Diseases and Infectious Diseases
7. Medical biotechnology and its therapeutic applications
8. Toxicology
9. Medical-biological defence research
10. Working conditions and health



Measuring coordination of leg movements.

1 Prevention and health care

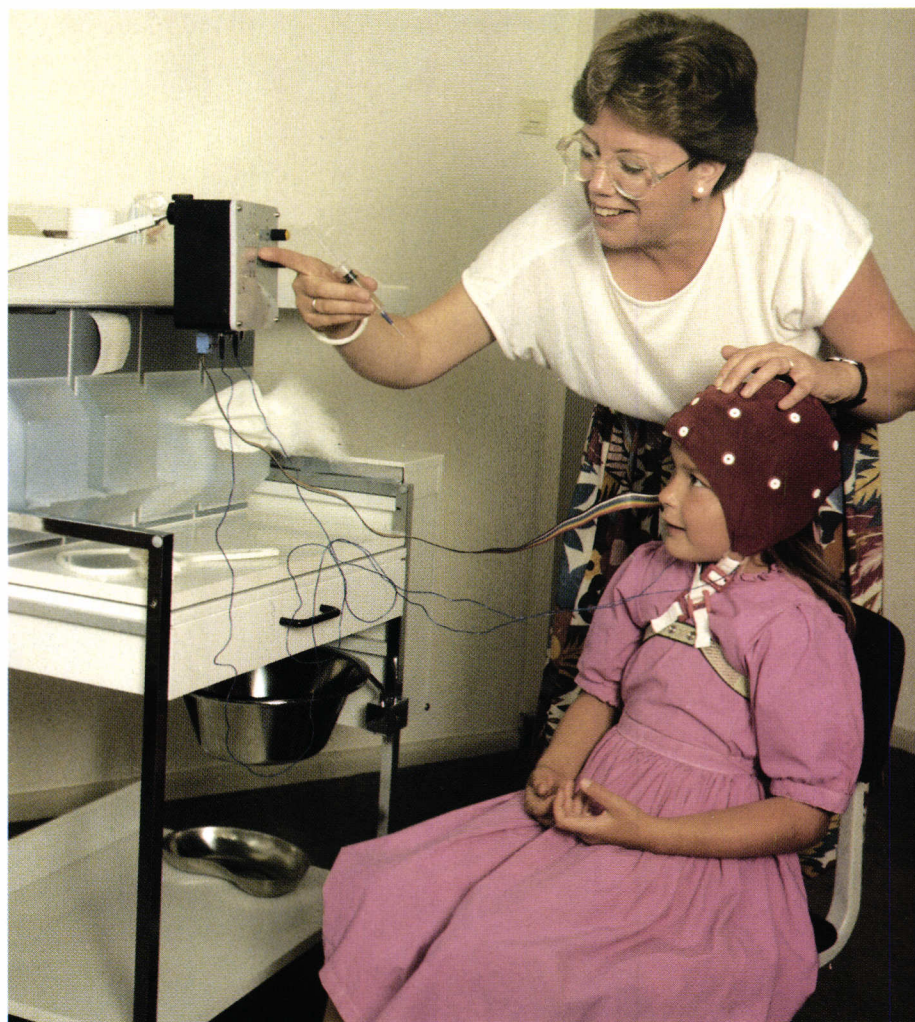
Public health

This TNO Health Research institute identifies and analyzes public-health problems by doing epidemiological and socioscientific research in relation to risk groups to support a preventive health-care policy. It develops and evaluates public-health programmes, procedures and methods in health-care systems, such as screening for congenital anomalies and cervical cancer, does research into cost-effectiveness aspects and supports public information programmes on, e.g., accidents and AIDS. Another task is research on the structure and performance of health services in the area of preventive health care. Examples are nursing services in public health and future 'scenarios' for community health care.

Child and adolescent health care

Health care of the young includes both preventive health care research and information and advice to the public. Research is done on the early detection of abnormal as well as normal growth and development and on health hazards and perinatal epidemiology. The objective is to gain a better understanding of the health of children and adolescents, the factors that influence their health and the possibilities for preventive measures. It seems that prevention is especially effective in young persons and has far-reaching effects up to a very old age. Special attention is given to socioeconomic features, ethnic backgrounds, lifestyles and living conditions.

A young girl in an experiment for a neurophysiological project; the registration of an electro-encephalogram (EEG).



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Dental care and epidemiology

Information on the importance of good oral hygiene and dental care is necessary to reduce caries and to prevent dental and oral-cavity diseases. TNO Health Research performs intervention studies and advises on the organization and accessibility of dental care. Data on oral hygiene are regularly evaluated on a national level.

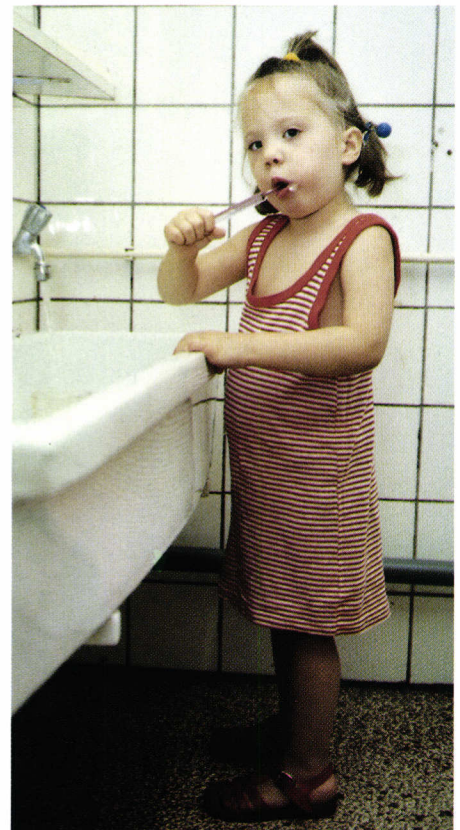
Postgraduate training

NIPG-TNO is responsible for postgraduate training courses on topics such as Public Health Care, Child Health, Occupational Health, Health and Environment and Public Health Administration. In addition, seminars and courses are organized on specific topics and postgraduate training is given to special groups such as physicians at childhealth centres and specialists in occupational medicine.



Safety in the home.

Dental care in children.



2 Gerontology

The increase in the proportion of old individuals and the associated accumulation of geriatric diseases will constitute the major medical-social problems of the near future.

In The Netherlands, the total number of people aged 65 years or older will have doubled within 40 years, while the number of those over 85 will have doubled even within 15 years. Consequently, there will be a growing demand for gerontological research in the next decade. Knowledge of general ageing processes and of ageing at the level of organs, tissues and cells (biomedical gerontology) is limited. Many problems relating to specific medical care for the elderly (geriatrics) have not been solved. Most questions in the field of geriatrics, including strategies for prevention, can be successfully addressed only if supported by biomedical gerontological research.

TNO Health Research occupies an important position in fundamental and applied biomedical research in the areas of age-related pathology,

immunogerontology, cell and organ physiology and molecular biology in The Netherlands, and in Europe through 'EURAGE', an EC 'concerted action programme'.

In addition, research is performed on the application of new materials and microelectronics that may alleviate problems in the home care and rehabilitation of geriatric patients.

Dementia

About one in ten senior citizens in The Netherlands becomes more or less affected by dementia. Fifty per cent of these cases result from Alzheimer's disease. In an ageing population, an increasing number of patients suffering from this debilitating disease can be expected. The diagnosis Alzheimer's disease can be made only at a relatively late stage of the condition, on the basis of exclusion criteria and can be verified only by postmortem examination. Therefore, TNO Health Research is doing research on improving the possibilities for diagnosing this disease at an earlier stage. Attention is being

Participant in the 'over 85 study'.

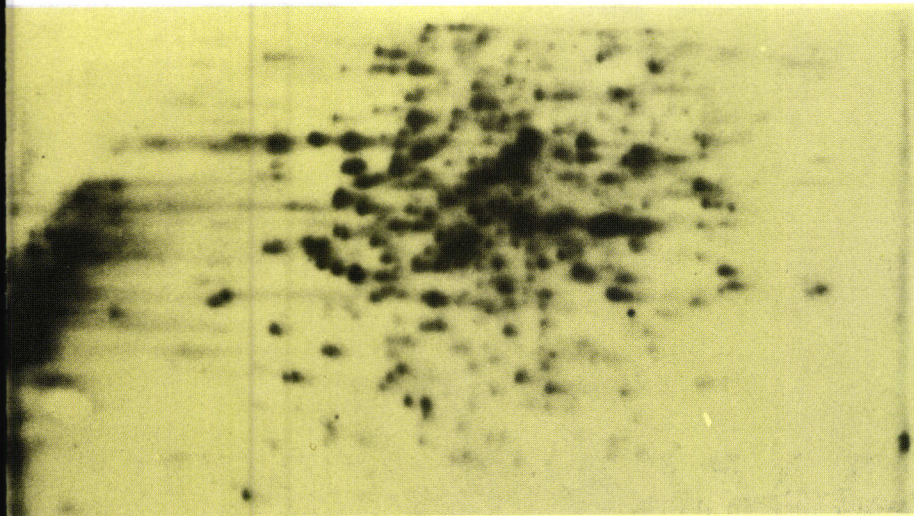


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focused on the development of advanced recombinant DNA (rDNA) techniques that allow fingerprint analysis of the mammalian genome for minute variations that might be involved in or predispose to certain deteriorative aspects of ageing such as Alzheimer's type of dementia. In addition, by studying the defective immune response of these patients, immunological parameters that could contribute to early detection and to an understanding of the origin of this type of dementia may be found. Furthermore, the diagnostic process may be facilitated by improved analysis of the electroencephalogram and by application of more sophisticated behavioural and psychological testing procedures.

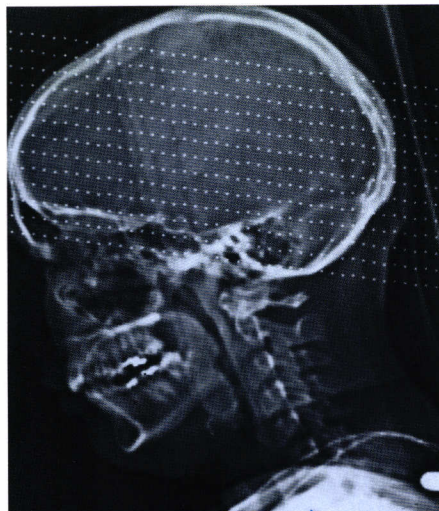
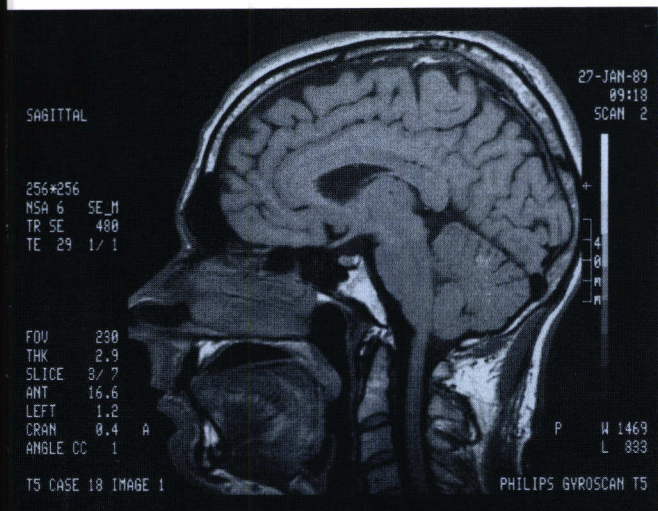
Osteoporosis

Like most other tissues, bone is subject to continuous turnover. If the rate of bone destruction exceeds that of bone formation, the bone mass may decrease over several decades to such an extent that clinical problems can arise (osteoporosis). This results in bone fractures under normal everyday conditions. Osteoporosis is especially common in postmenopausal women and deteriorates with age. This condition becomes more and more important with increasing numbers of surviving individuals. Research of TNO Health Research is focused on the effects of food components (such as vitamins), hormones, and growth factors to prevent or ameliorate senile and postmenopausal osteoporosis.



Example of modern DNA analysis: 'DNA fingerprinting'. DNA fragments are separated by electrophoresis. TNO possesses a patent on a special application of this two-dimensional separation technique.

Human brain imaging. On the right a CT (computer tomography) and on the left a MR (magnetic resonance) scan. In this way abnormal patterns that may occur in certain brain diseases, for instance Alzheimer's disease, can be visualized.



Effectiveness of drugs

Unwanted side effects of drug treatment sometimes resulting in hospitalization are frequently observed in the elderly. The cause of this problem is primarily the existence of a wide variety of individual reactions to the same drug resulting from differences in either metabolism of the drug or sensitivity of the target tissue. In order to assess appropriate therapeutic dosages in the elderly, methods are being developed to determine the extent of these two processes on an individual basis.

Ageing and immunology

The immune system plays an essential protective role in infectious diseases and can play a role in the host defenses against tumours. As an individual ages, the immune system becomes weaker. As a result, morbidity and mortality due to infectious diseases are high in the elderly. Detailed analysis of these deficiencies and their causes is required to prevent such diseases and their complications or to provide suitable therapeutic adjustments.

Osteoporosis.

Plastic sections of the tibia of young (6 month-old, left), and aged (29 month-old, right) female rats. Note age-related decreased number and width of bone trabeculae.



Nutrition and the elderly

Both the composition and the energy value of food have a great impact on the process of ageing. TNO Health Research studies the relationship between nutrition and major biochemical conversion processes in the body that affect ageing. The generation of free radicals and the processing of lipoproteins and cholesterol are subjects of investigations related to arteriosclerosis.

Independent existence

Regarding the independent existence of ageing persons, biomedical as well as social and psychological aspects have to be considered. In this respect, special attention is paid to the quality of first-line health care and special facilities for the elderly.



3 Cardiovascular research

Cardiovascular diseases are a major cause of illness and death in the western world. Two processes may be distinguished:

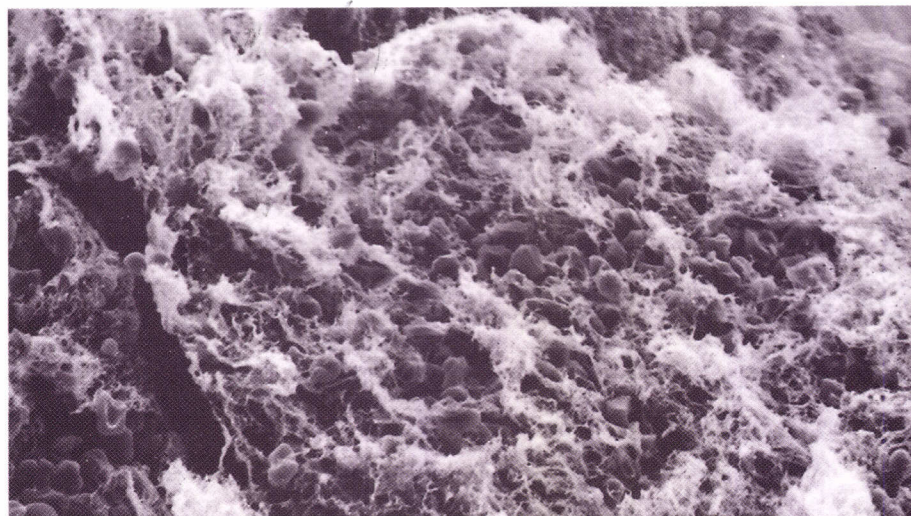
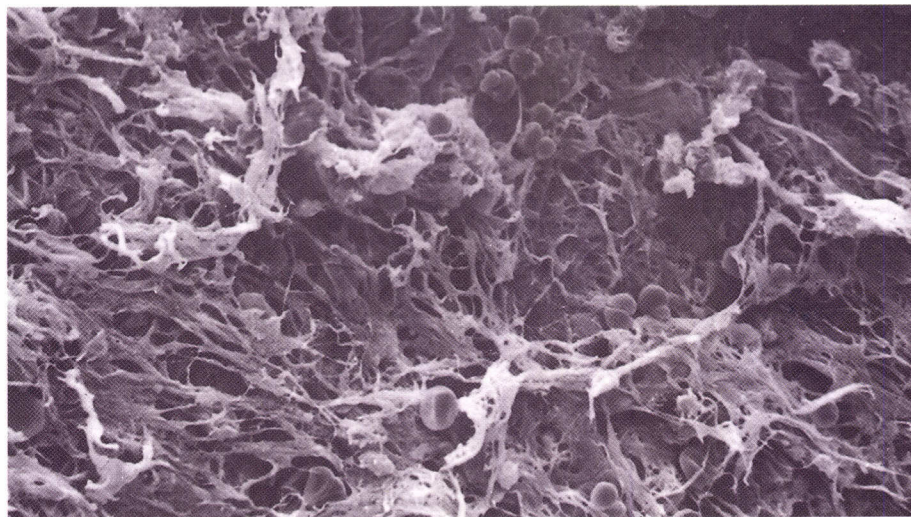
- alterations in the vascular wall caused by abnormalities in fat, lipoprotein and fibrinogen metabolism resulting in arteriosclerosis;
- disorders in the process of coagulation and in the removal of blood clots that may lead to thrombosis in arteries and veins, resulting in occlusion of the legs, stroke or myocardial infarction (heart attack).

Arteriosclerosis

An early onset of arteriosclerosis in major and minor arteries throughout the entire body, and particularly in the coronary arteries, occurs in persons with increased concentrations in the blood of low-density lipoproteins (LDL), mainly containing cholesterol, and in patients with a reduced concentration of high-density lipoproteins (HDL). Increased concentrations of fibrinogen increase the risk of arteriosclerosis.

Both the synthesis and catabolism of cholesterol and fibrinogen take place primarily in the liver. TNO Health Research studies the synthesis and catabolism of cholesterol and the interaction of LDL and HDL with the cells of the vascular wall (especially endothelial cells) and with liver cells.

Electron microscopic image of part of a blood clot containing fibrin threads: intact (above) and in the process of dissolution as a result of thrombolytic therapy (below).



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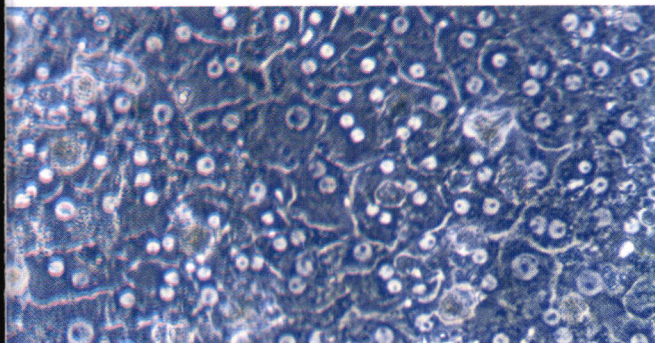
The protein components of lipoproteins, the apolipoproteins, play an essential role in these processes. In studies using laboratory animals and human liver cells in tissue cultures, a search is made for drugs which slow down detrimental processes in the vascular wall.

Therapy of vascular thrombosis

Pharmacists and physicians are very interested in somatic enzymes that are able to break down clots in the bloodstream, a process called fibrinolysis or thrombolysis. A key role in this process is played by tissue-plasminogen activator (t-PA) which is very effective as a highly specific thrombolytic drug. This

t-PA and a number of 'second generation' thrombolytics with improved properties are produced in cultured human and animal cells. They are tested for their effectiveness in dissolving blood clots both *in vitro* and in animal models *in vivo*. The effectiveness of thrombolytic agents in preventing myocardial infarction in humans is investigated in cooperation with a number of clinics.

Research is also being carried out on the mechanisms, synthesis and degradation, transport through the body, specificity and mutual interaction of t-PA and pro-urokinase, another natural plasminogen activator.



Human liver cells.



The commercially available Fibrinostika-kit.

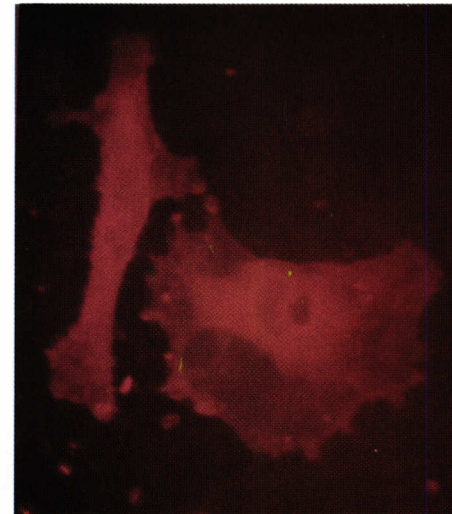
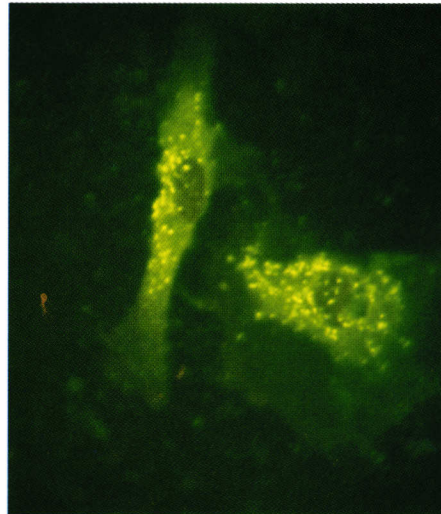
Early detection of thrombosis

The early stages of clotting and thrombosis in the body can be inferred before clinical complaints become manifest from the presence of degradation products of plasma proteins in the blood, such as fibrinogen and fibrin. In cooperation with partners from industry, methods based on the application of monoclonal antibodies are being developed in order to demonstrate the presence of these plasma proteins and fibrin-degradation products accurately and automatically. OTNO, the joint venture of Organon Teknika (OT-AKZO) and TNO, has commercialised a number of these new diagnostics for a variety of diseases.

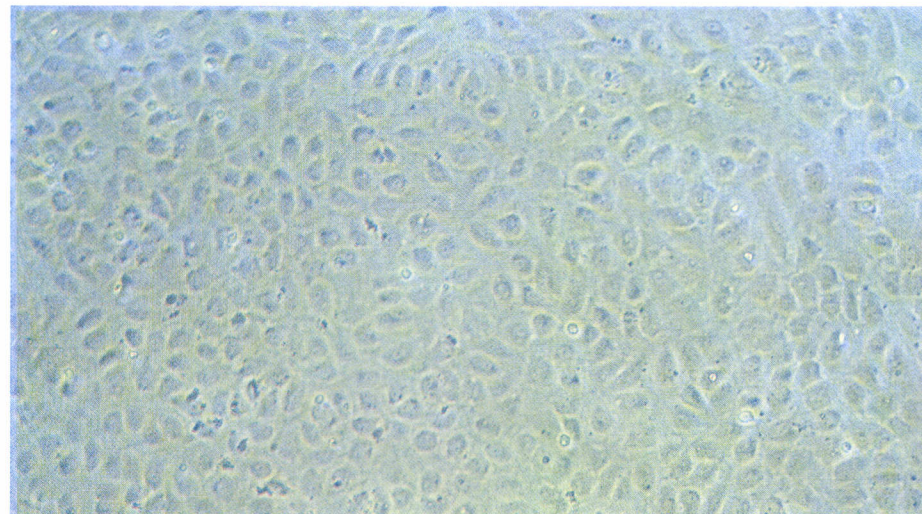
Endothelial cell function

The thin layer of cells covering the inside of all blood vessels (endothelium) is involved in a very large number of processes, amongst others in the regulation of the passage of fats and proteins through the vessel wall and in the production of agents that control clotting and fibrinolysis and blood pressure. TNO Health Research studies the production of these agents such as t-PA and its inhibitor by comparing healthy endothelium from animals as well as from humans and endothelium that is pathologically altered as a result of vascular disease and chronic infections. The possibility of influencing endothelial functions is also being investigated.

Fluorescence microscopic images of: left (yellow) cells with the Von Willebrand Factor, and right: (red) the bonding of *Ulex europaeus* lectin. The Von Willebrand Factor is released from the small organelles after stimulation of the cell, and plays a role in the interaction of platelets with the vascular wall.



Monolayer of human endothelial cells seen through a phase-contrast microscope.



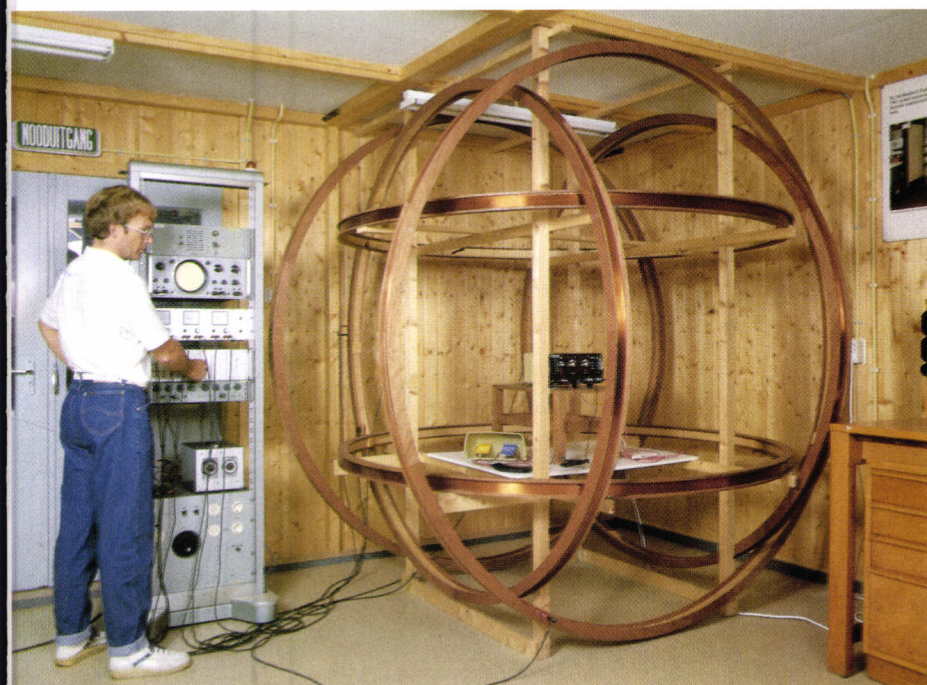
4 Medical technology and rehabilitation

Medical technology

The attention of TNO Health Research is focused on stimulating the use of appropriate, safe and reliable medical equipment and on evaluating such equipment and provisions. The wide range of medical technological products raises an increasing amount of questions on responsible acquisition and application. Producers of medical equipment can find advice on quality improvement and innovation. In addition, TNO Health Research provides testing facilities and is familiar with the standards and admission regulations that apply in different markets.

Rehabilitation and technology

This area of research in TNO Health Research concentrates on improving technical facilities for disabled people and for use in rehabilitation. Rehabilitation is the coordinated and combined use of facilities in medical and social fields to assist a disabled person to fit into society (again) in the best possible way. Special attention is paid to technological developments for the benefit of disabled workers. Such research is carried out in close cooperation with the Institute for Rehabilitation Research at Hoensbroek (IRV) and coordinated by the TNO Committee on Rehabilitation Engineering Research.



Testing the sensitivity of medical equipment to magnetic fields (50 Hz).



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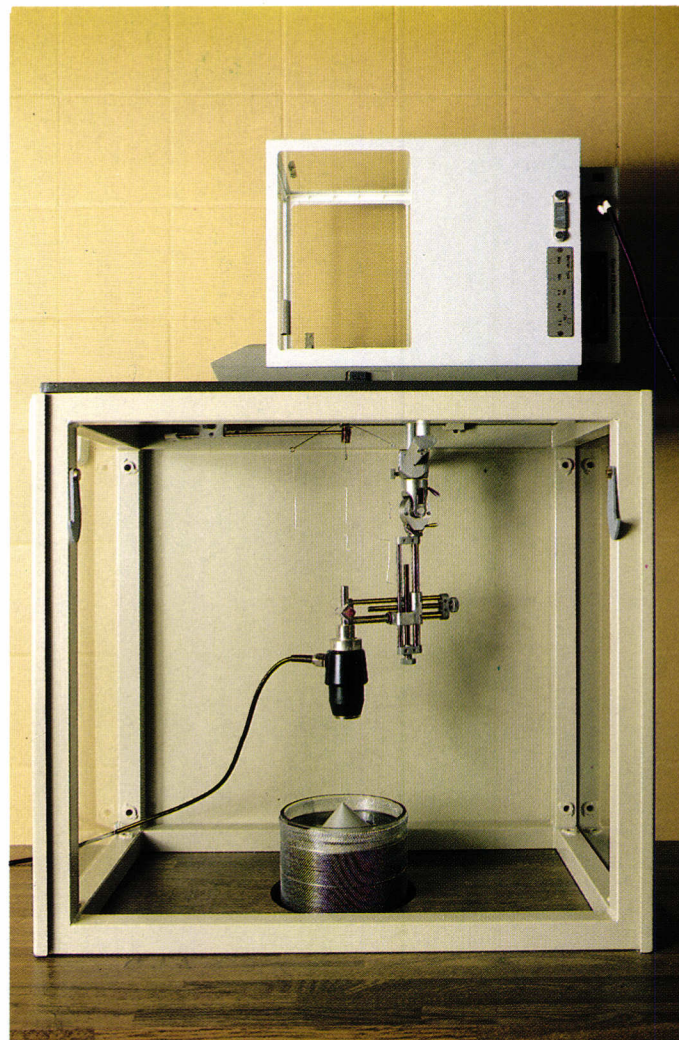
Medical technology assessment

Research designed to collect data required for formulating policy decisions is called technology assessment (TA). As regards decisions concerning medical technology, cost-effectiveness is an important aspect; but, managerial, social and ethical aspects are also important. Knowledge available in TNO Health Research on existing methods or future developments forms the basis of cost-benefit analyses. Organizational aspects are evaluated, technologies are assessed and health-care needs are analyzed to determine priorities for research. In this area, cooperation with other institutes and universities is of prime importance. Some examples

are a cost-benefit analysis of population benefit analysis of population screening for breast cancer, early diagnosis of Alzheimer's disease (see also Gerontology section), indications of the tendency to thrombosis, effectiveness of ultra-sound in physiotherapy and the effectiveness of various laboratory and physiology tests.

Measuring effective ultrasound potential with a radiation-pressure balance.

MediMatica: an easily accessible data bank.



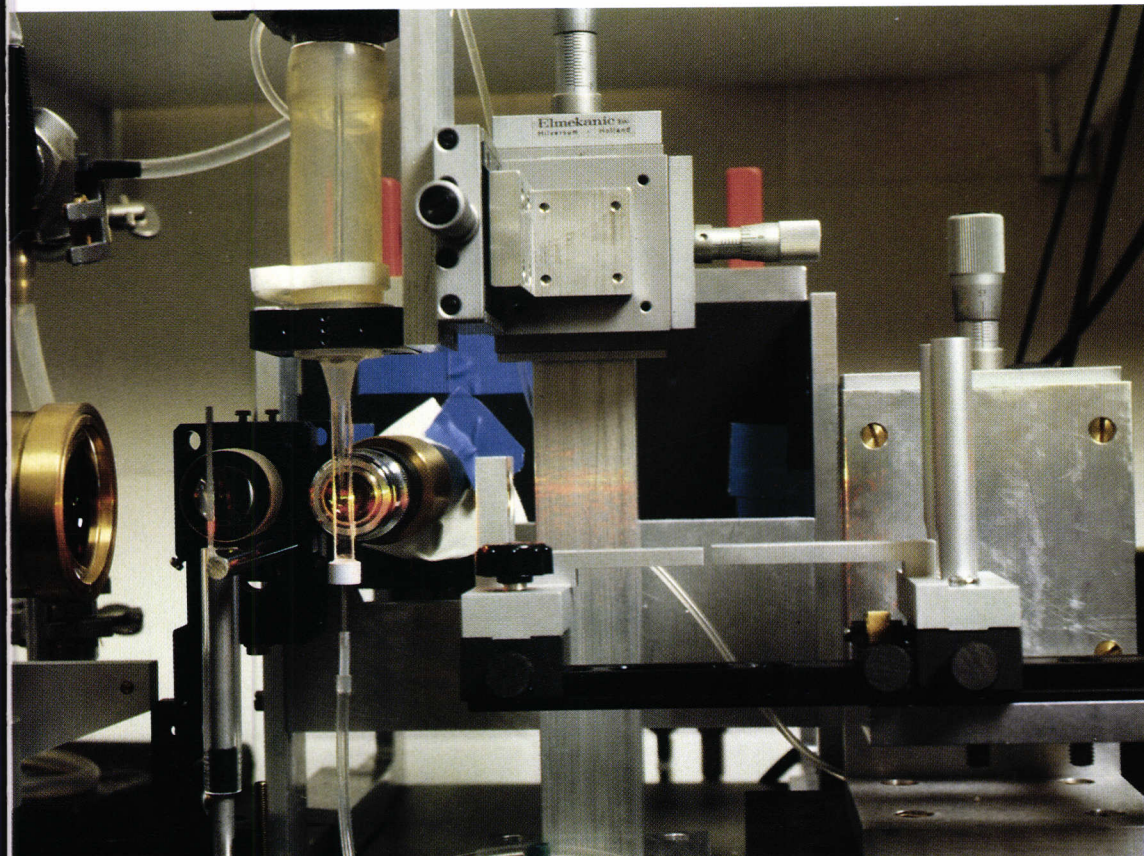
Computerization of medical information

The importance of computerization of medical information in health care is growing rapidly. This information technology already gives scientists access to data in professional literature collected over many years. Computerization of medical information will become an even more important tool in diagnoses and practical clinical epidemiology when expert systems become available in the near future. TNO Health Research, in close cooperation with the TNO Institute of Applied Computer Science, advises on new developments in this field. During the next few years, the emphasis will be on making medical computerization and information technology available for use in first-line health care.

Biomedical analysis

Formerly, it was necessary to construct equipment for medical-biological research 'on the spot' in laboratories. Nowadays, a wide range of equipment is commercially available. Relieved of the task of building all its equipment, TNO Health Research now develops only high-tech equipment that is not available commercially. Examples are a system to quantify posture and movement in ergonomics; equipment to test behaviour in laboratory animals; a system to analyse and sort individual cells with help of flow cytometry and the analysis of individual cells using laser scan microscopy.

An example of high-tech equipment not commercially available: the Optical Plancton Analyzer (OPA) designed and built by RBI-TNO for the department of Aquatic Oecology of the University of Amsterdam.



5 Radiation and health

Radiobiology and risk assessment

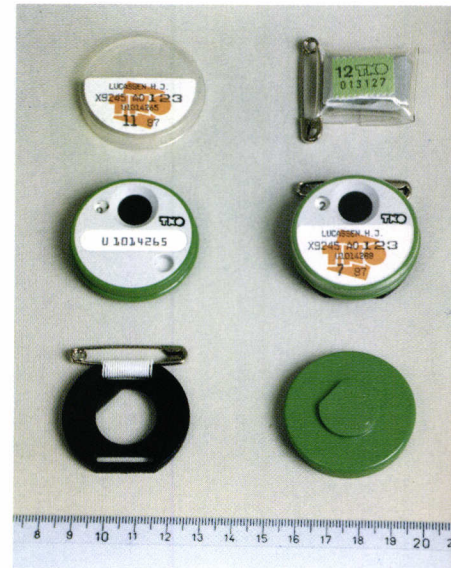
The risk of developing cancer following exposure to low levels of ionising radiation during occupational activities or diagnostic/therapeutic procedures is being studied as such and in combination with exposure to other agents. Low levels of radiation can damage DNA in circulating blood cells. A system of biological dosimetry based on the quantitative determination of DNA damage in these cell types is being developed.

Exposure to high doses of radiation causes severe damage to the hemopoietic system. To improve treatment in radiation accidents TNO Health Research is studying methods for improving radiation dosimetry and for better radiation diagnostics for application to bone-marrow transplantation procedures.

Radiation protection and dosimetry

The expertise of TNO Health Research in the area of ionizing radiation has led to an extensive advisory function to the government, hospitals, industry and private individuals on the subject of radiation protection and dosimetry. Further development and introduction of protocols for dosimetry in radiobiological research and radiotherapy will contribute substantially to a greater precision and improved reliability of the applications of radiation in health care.

Individual radiation dosimetry: the traditional film badge (top right) and the recently developed TLD badge (thermo luminescence dose meter).



Example of a model for improving radiation dosimetry.

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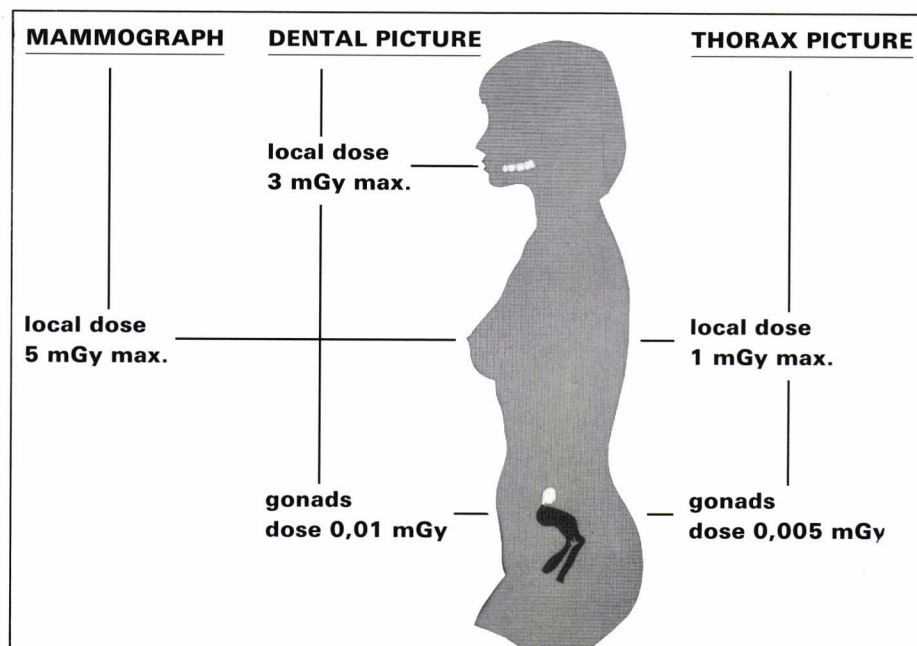
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The TNO Radiological Protection Service (RD-TNO) in Arnhem is mainly involved in practical radiation protection. RD-TNO supplies personal dose meters for the individual monitoring of radiological workers (about 20,000 in The Netherlands).

The results are recorded and stored in a data bank operated by TNO: the National Dose Registration and Information System (NDRIS).

As part of its R&D activities, TNO Health Research has developed a fully automated thermoluminescence dosimetry (TLD) system for individual monitoring.

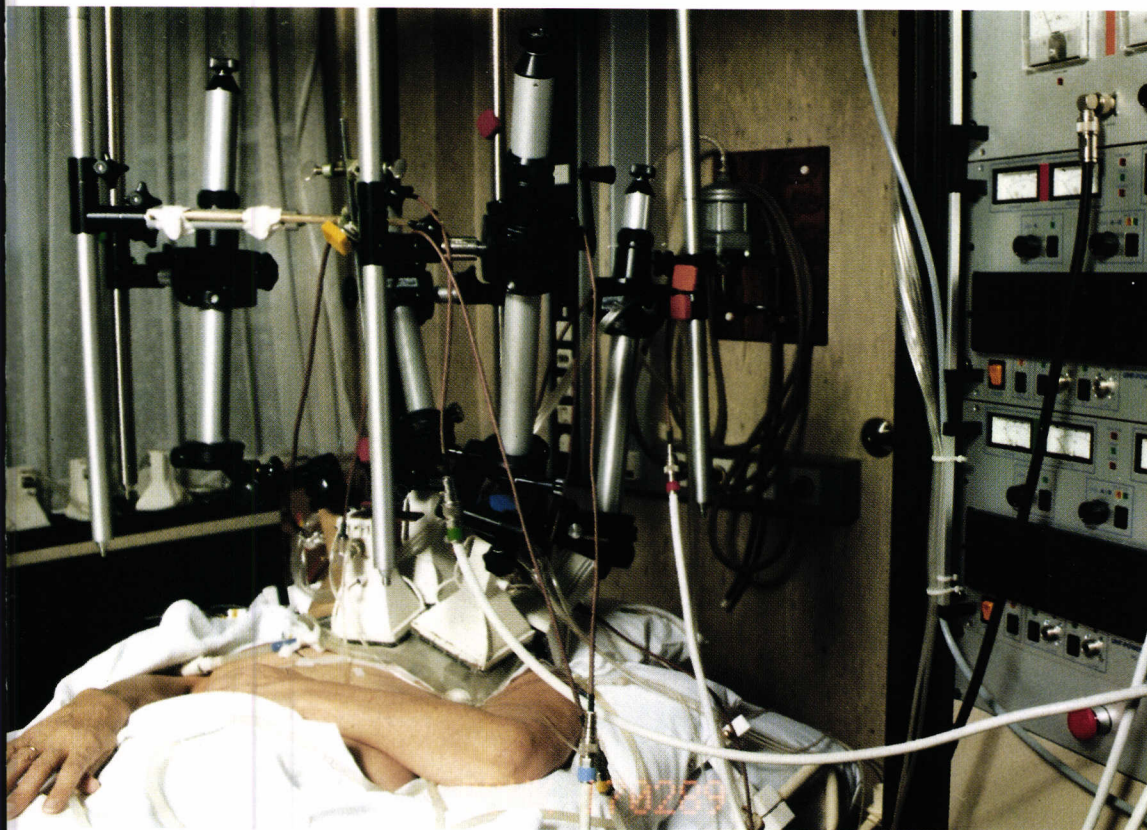
RD-TNO also provides services to third parties such as radiation-safety investigations, quality assurance measurements in diagnostic radiology departments and gives advice on shielding and calibration of measuring instruments.

Radiotherapy

To develop new treatment methods, radiotherapy models employing laboratory animals that have essentially the same response characteristics as human tumours are required. TNO Health Research has been successful in developing such animal experimental models for various types of lung tumours and leukemia. These models have been used to study the selection and application of optimum combinations of radiotherapy, chemotherapy and/or hyperthermia. Since therapeutic doses are often damaging to normal tissues, their sensitivity to restricted doses of radiation is studied, in particular muscle, kidney and lung tissues.

Finally, TNO Health Research contributes to the discipline by offering educational and training programmes for radiotherapists.

Hyperthermia, treatment of a patient suffering from a relapsed breast cancer with microwave equipment. At the right in the background the 433 MHz generators.



6 Chronic and infectious diseases

Chronic debilitating diseases are sources of prolonged human suffering. Because of their persistent and recurrent nature, such diseases place a very heavy burden on society. They are frequently incurable, requiring long-term patient care and expensive therapy. They are major causes of physical disability and mortality. In The Netherlands, diseases of the cardiovascular system, arthritis and neurological disorders are the most common chronic diseases. These and age-related diseases, cancer and especially contagious diseases are the major focus of research programmes at TNO Health Research. European cooperation is being pursued in the areas of arthritis and neurological research to develop a strong multidisciplinary effort.

Arthritis

Rheumatoid arthritis is a chronic disease of the joints. The immune system is involved in the development of this form of incurable and debilitating disease. The cause of various types of arthritis is unknown. About twenty per cent of the senior citizens in The Netherlands suffer from arthritis or rheumatoid inflammations of the joints. Therapeutic drugs are capable of slowing down the development of arthritic lesions to some extent; but, because high doses are needed, the side-effects are significant. Medicinal treatment is largely unsatisfactory in preventing disease progression. TNO Health Research endeavours to contribute to the knowledge on the origin and prevention of arthritis. A model has been developed in rhesus monkeys to study individual sensitivity to immune arthritis-inducing agents. In this model, potential

The hands of an arthritic rhesus monkey. (30 days after immunisation with collagen type II.)



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drugs such as compounds that inhibit infections in general are being tested for effectiveness. In addition, substances that regulate the immune system (e.g., interferon and interleukins) and inhibitors of protein- and fibrin-degradating enzymes are being tested for their potential therapeutic application. By choosing a primate as a model, it is expected that results will be relevant and easily extrapolated to various forms of human disease. Moreover, anti-arthritic drugs can be screened more rapidly and approved for human trials after testing in nonhuman primate models. The Committee on Arthritis Research, to which members of TNO Health Research belong, coordinates and evaluates research programmes on arthritis in The Netherlands as a contribution to the development of strategies to prevent and cure arthritis.

Multiple sclerosis

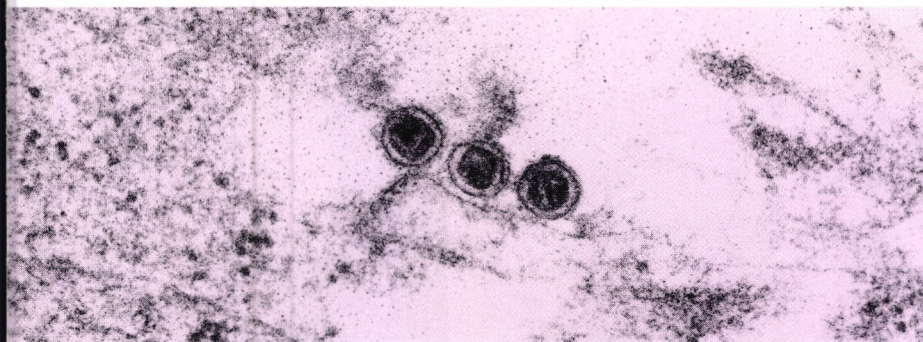
Multiple sclerosis (MS) is a chronic disease resulting from slow degeneration of the nerves of the central nervous system. There is clinical and experimental evidence that the part of the immune system that plays a role in the rejection of foreign tissue may suppress experimentally induced MS.

Epilepsy

The underlying causes of epilepsy are the area of activity of the TNO Committee National Epilepsy Research (CLEO). It coordinates and evaluates research programmes on epilepsy in The Netherlands.



Interferon: a product of biotechnology. Rat cytokines produced using recombinant DNA-manipulated cell strains.



Three retrovirus particles known to be capable of causing T-cell leukemia. According to the latest opinion, related virus particles are suspected to play a role in autoimmune diseases and neurological disorders such as multiple sclerosis.

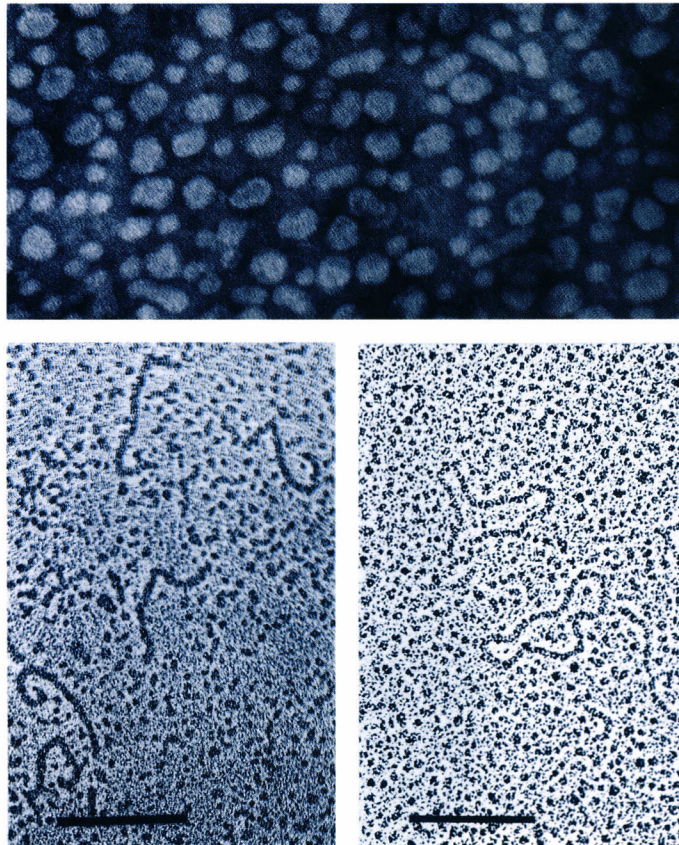
Infectious diseases

The decrease in childhood mortality and the increased life expectancy over the past century are mainly due to the fact that infectious diseases claim fewer victims. Such diseases are caused by contagious microorganisms. In combination with improved hygiene, medical science has made perhaps the most significant contribution to promotion of health by reducing infectious diseases through the development of specific vaccines and antibiotics. However, since cures for many of these diseases has been found, a new generation of infectious diseases has come to the forefront and existing ones present a more serious problem. These include conditions such as Legionnaires' disease, hepatitis, genital Herpes and AIDS. TNO Health Research has research programmes on AIDS, hepatitis, parasitic diseases (malaria and filariasis) and tuberculosis.

AIDS

The research programme on AIDS (acquired immune deficiency syndrome) is concentrated on the epidemiology and the therapy of this disease. It is known now that AIDS is a viral infection characterized by a chronic incurable disease course, rendering the immune system incapable of protecting the patient from common opportunistic infections that eventually cause death. Because the immune system is primarily affected, TNO Health Research devotes much research effort to understanding the factors that make it susceptible to attack. Chimpanzees play an important role in this research, since they are the only animals susceptible to infection by the human AIDS virus (HIV). However, HIV is not able to induce immunosuppressive disease in chimpanzees as it does in man. The chimpanzee's immune system is somehow resistant to the disease. The animals

Example of hepatitis delta virus.
Left: RNA of the virus in normal conditions.
Right: RNA in extreme denaturation conditions. Denaturation prevents internal base coupling, suggesting that the RNA is a closed circle.



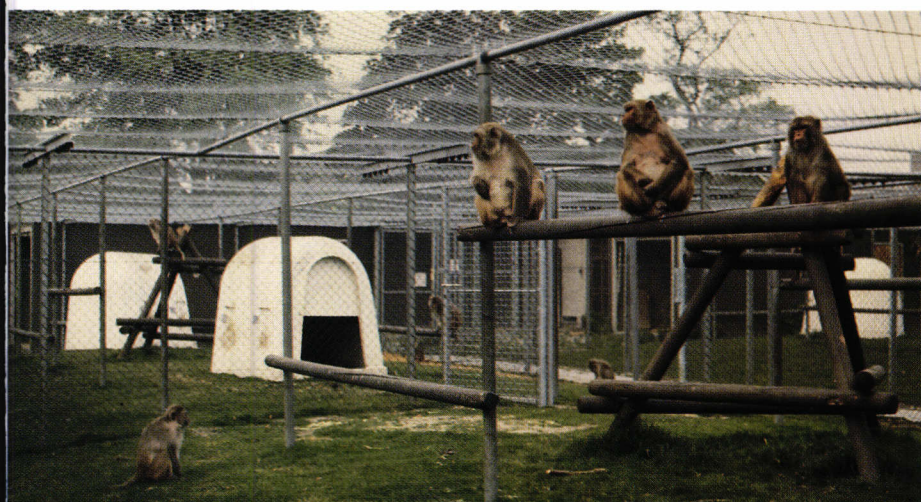
For the daily care of sick chimpanzees protective clothing is compulsory.



remain immunologically competent and able to combat normal opportunistic pathogens. It is reasoned that understanding the chimpanzee's immune system and its ability to resist the effects of HIV may lead to a cure for infected humans. The chimpanzee colony of the Primate Center of TNO is structurally available for European research on HIV. In parallel with investigations on HIV, an AIDS model is being developed in rhesus monkeys with SIV (simian immunodeficiency virus). Epidemiological research on AIDS supports governmental policy in relation to information and educational activities.

Addiction

The use of addictive drugs is a serious social and medical problem. TNO Health Research investigates damage to the nervous system and gastro-intestinal system (including the liver) as a result of the use of alcohol and the abuse of organic-solvent vapours. Animal experiments to study the cause of alcohol addiction have been started. Drugs that influence reward centres in the brain are being tested for their potential use to break drug dependence.



The Primate Center of TNO Health Research possesses facilities for its monkey colony that are unique in the world.



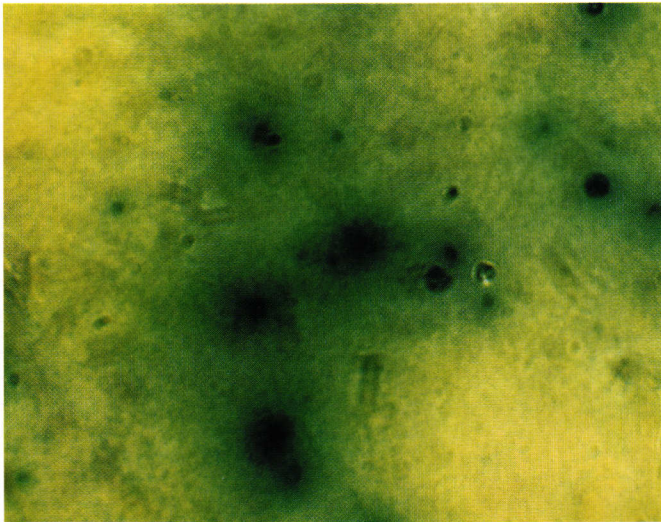
Set-up to study whether drugs can prevent alcohol consumption.

Hepatitis

This research mainly involves the development and testing of vaccines against hepatitis B, delta and nonA nonB. The application of monoclonal antibody procedures and recombinant DNA techniques has resulted in rapid progress and many important breakthroughs in the case of hepatitis B. It is likely that the same will be true for other hepatitis viruses in the near future.

Biological Response Modifiers

Interleukins and interferons are among the biological response modifiers (BRMs) occurring naturally in the human body. TNO Health Research

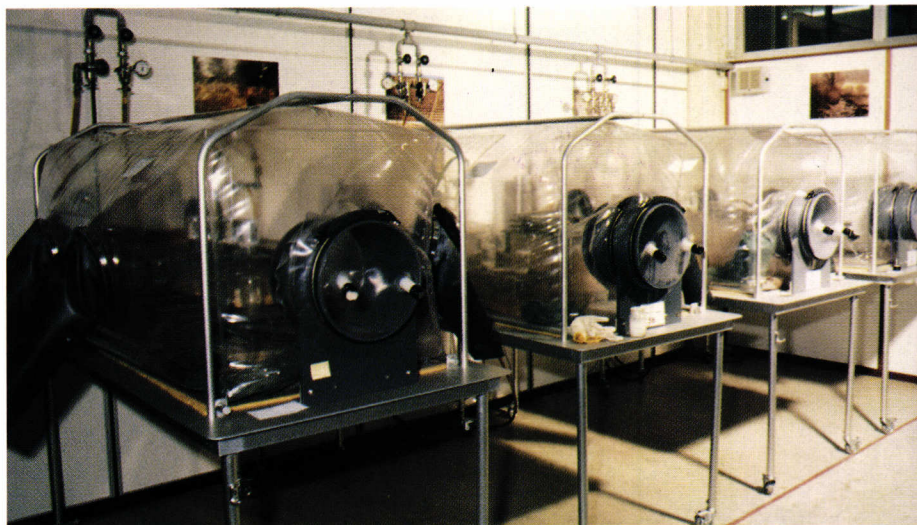


Light microscopic picture of interferon-gamma-producing T-lymphocytes. Interferon is made visible by specific monoclonal antibodies linked to an enzyme that changes a colourless substrate into a blue reaction product.

studies the production and effect of interferons and other cytokines. The mode of action and the potential uses of BRMs in the treatment of viral infections and in cancer therapy are essential parts of those studies.

Laboratory animals

In experimental medical research, the selection of a biological system is critically important. Research on specific diseases and suitable therapies necessitates the use of animal models. If it is possible and acceptable to test directly in humans or in *in vitro* systems, this approach is generally preferred. However, much of the research on new forms of therapy or possible health risks can only be carried out by using laboratory animals. The facilities at the Primate Center of TNO for research on primates are unique worldwide. For more than 25 years, chimpanzees and rhesus monkeys (*Macaca mulatta*) have been bred under strictly controlled and well-defined conditions. The colony of TNO Health Research is well characterized on the basis of tissue types and is maintained by selective breeding. About 100 chimpanzees and 1000 macaques are housed in the Primate Center of TNO. These animals are used for preclinical trials of well-characterized minimal-risk preparations such as biotechnologically prepared vaccines and therapeutics for both national and international pharmaceutical industries. High-standard facilities are available to produce and house rodents under pathogen-free conditions. This is of prime importance in understanding the role of microorganisms in such medical procedures, as transplantation, radiation and arthritis research.



TNO Health Research has facilities to breed rodents in germ-free conditions.

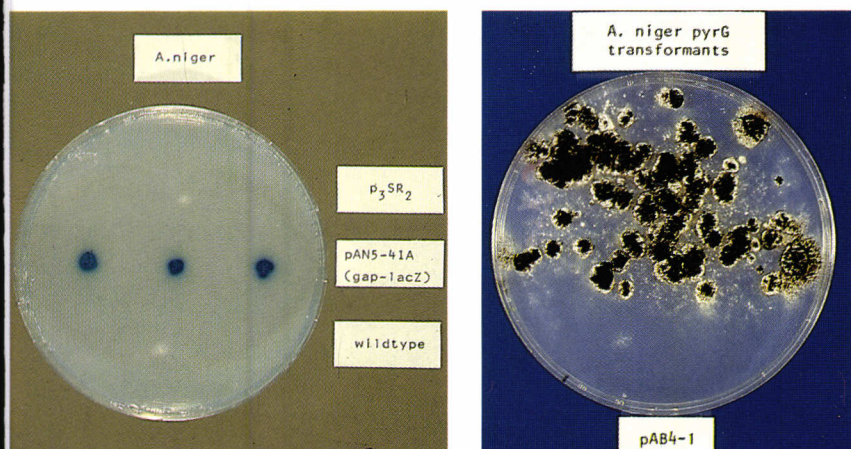
7 Medical biotechnology and its therapeutic applications

Medical biotechnological research requires special laboratory facilities, which are available at TNO Health Research institutes. For recombinant DNA studies, physical containment can be achieved up to the level of C-III (P-III). For studies on the expression of genetic information and on mutagenesis in mammalian cells *in vivo*, transgenic mice are bred that carry selected DNA sequences in their chromosomes. Ample facilities for breeding and housing nonhuman primates and rodents are available to test the activity and safety of recombinant DNA products.

In recent years, interest in the synthesis of substances of medical importance by genetically altered microorganisms or cultured mammalian cells has greatly increased. DNA technology now enables the production of materials that cannot be produced economically by conventional methods. Applied

research at TNO Health Research aims at the development of DNA technology for fungi (*Aspergillus*, *Penicillium*) and lactic acid bacteria (*Lactobacillus*) for use in the pharmaceutical and fermentation industries.

DNA technology is also used intensively for the production of blood proteins, biological response modifiers (BRMs) and enzymes. Examples are the production of the thrombosis-suppressing protein plasminogen activator, various interferons (which can be used to combat virus infections) and interleukins (important, for instance, in treating bone-marrow damage caused by radiation or chemotherapy). In attempting to find new approaches for the production of vaccines, the coat proteins of infectious viruses causing foot-and-mouth-disease, poliomyelitis and hepatitis delta are modified by genetic engineering and utilized to produce highly purified virus antigens without including the entire infectious virus.



Left:

By incorporating an efficient control element *Aspergillus* strains can be obtained that possess a hundred times higher concentration of certain enzymes. This particular enzyme is made visible by a blue staining.

Right:

Aspergillus niger, a fungus that can be used as a hostvector to introduce foreign genetic material into organisms. MBL uses this fungus in particular for the production of enzymes.



In this new DNA laboratory of MBL, physical and biological containment can be realised up to the C-III level. Most activities require lower safety limits.

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Within a few years, DNA technology applied to mammalian cells will open the way to gene therapy. This strategy is based on the correction of genetic defects by supplying cells with new (healthy) genes. Techniques for gene therapy are being developed to cure congenital diseases such as severe combined immune deficiency by adding the correct version of the gene to the bone-marrow cells of patients. This is done by infecting bone-marrow cells with retroviruses that contain the missing gene and can introduce it into host-cell chromosomes, thus enabling the progeny of these cells to produce the correct cell product. It is expected that this technique can be applied clinically within 5–10 years.

Biomolecular diagnostics

The specific detection of complex biological structures is another potentially successful cornerstone of medical biotechnology. The extreme precision of an antibody in recognizing its corresponding antigen and that of a DNA probe in recognizing complementary DNA, is currently being used for several analytical and diagnostic purposes.

Proving the existence of thymidine dimers with immunofluorescence microscopy.

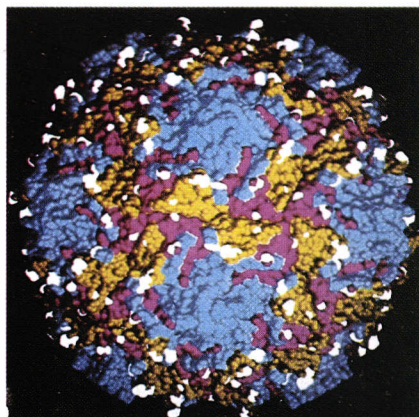
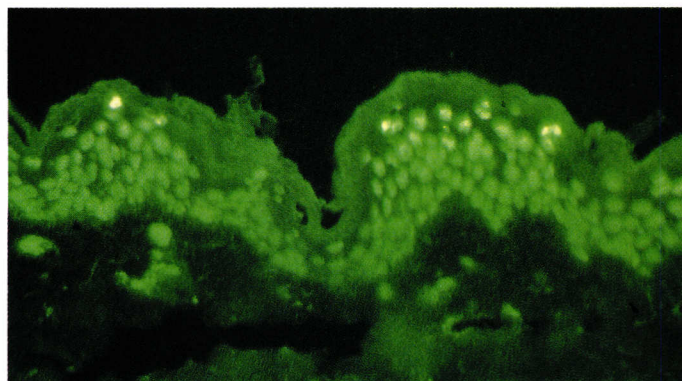
Above: a biopt incubated with monoclonal antibodies aimed specifically at thymidine dimers. Afterwards a fluorescing reaction agent was added to stain the thymidine spots green.

Below: the same biopt now stained for total DNA with propidium iodide.

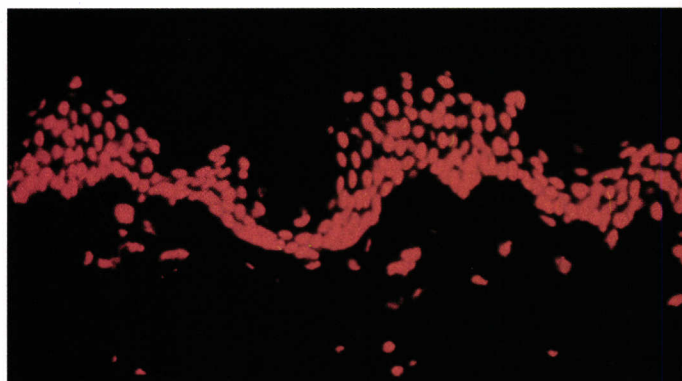
The application of antibodies and DNA probes for medical diagnostics is being investigated for purposes of:

- detection of hepatitis delta infection;
- detection of the AIDS virus and AIDS proteins;
- detection of DNA modifications caused by exposure to genotoxic agents;
- detection of genetic changes in cancer cells;
- detection and application of interferons;
- preparation of selective antibodies against specific classes of related biological proteins using synthetic peptides;
- detection of variations in fibrin- and fat metabolism indicating a risk of cardiovascular disease (see also Section 3).

New horizons in immunotechnology are being explored in studies on the way in which a foreign substance (antigen) is presented to the immune system. It is expected that improvement of that presentation will result in better techniques for vaccine preparation.



A computer model of the polio virus. Different colours indicate different envelope proteins.



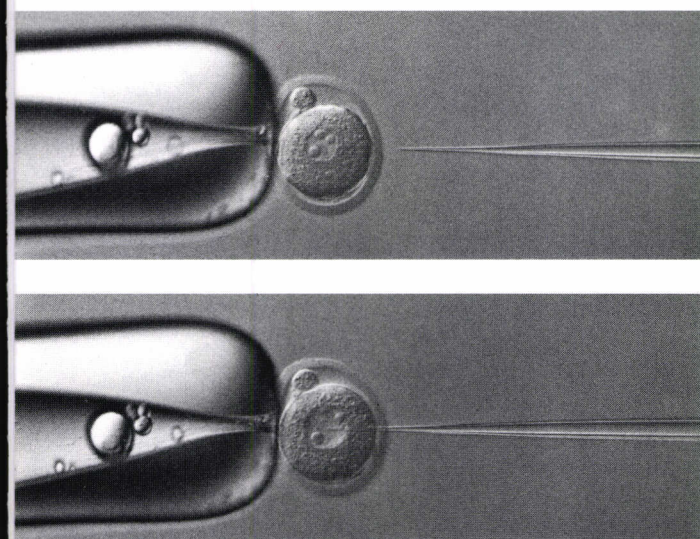
8 Toxicology

As a result of industrialization, man is exposed to a wide variety of chemical compounds in both living and working environments. Occupational exposure to very toxic compounds is usually accompanied by far-reaching measures of a technical or hygienic nature and in the field of occupational health care. However, the question remains whether a possible residual exposure can be considered an acceptable health hazard. In most cases, occupational exposure involves compounds that do not possess extreme toxic properties. However, even in these situations, the existence and extent of a potential health hazard should be ascertained.

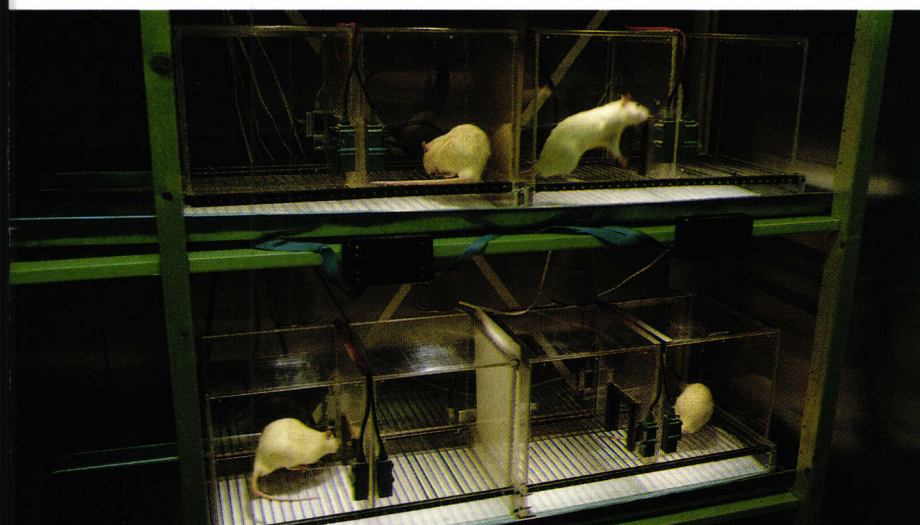
Genetic toxicology

In the area of genetic toxicology, the effects of radiation and chemicals on DNA are studied. At the cellular level, damage to chromosomal DNA may lead to cell death, to reduced mitotical activity or to a permanent genetic modification (mutation). In the latter case, the progeny of a damaged cell shows the same mutation. In higher organisms, mutations may lead to the development of cancer, but might also contribute to the process of ageing. Mutations in reproductive cells may lead to congenital defects and diseases.

The repair mechanisms of cells are normally able to cope with DNA damage. Misrepair sometimes occurs, resulting in a permanent mutation. Age-dependent



Light microscopic picture of two phases of injection of 'foreign' DNA into a fertilized mouse ovum. The cell is kept in position by the pipette on the left while the micropipette on the right inserts DNA into the nucleus.



'Shuttle box' set-up. When the light switches on over the compartment in which the rat is present, this animal has to go to another compartment within ten seconds. This process is repeated several times and the results are registered.

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deterioration of this repair capacity and fidelity may be responsible for the accumulation of mutations in the elderly.

With an extensive range of highly sophisticated microscopic and immunological techniques (including laser scan microscopy), monoclonal antibodies and flow cytometry, many problems in the area of genetic toxicology are systematically studied. The main research objective is to determine what types of DNA damage are the most detrimental to health.

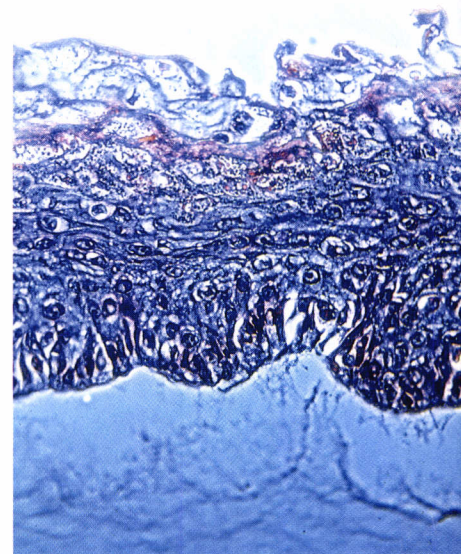
TNO Health Research develops clinically applicable methods for detecting and quantifying DNA modifications in human white blood cells and other cell types after exposure to agents that may damage DNA. Research concentrates on changes in DNA that may arise after exposure to genotoxic compounds either at work or as a result of treatment with chemotherapeutic agents or after intensive accidental radiation.

Dermal toxicology

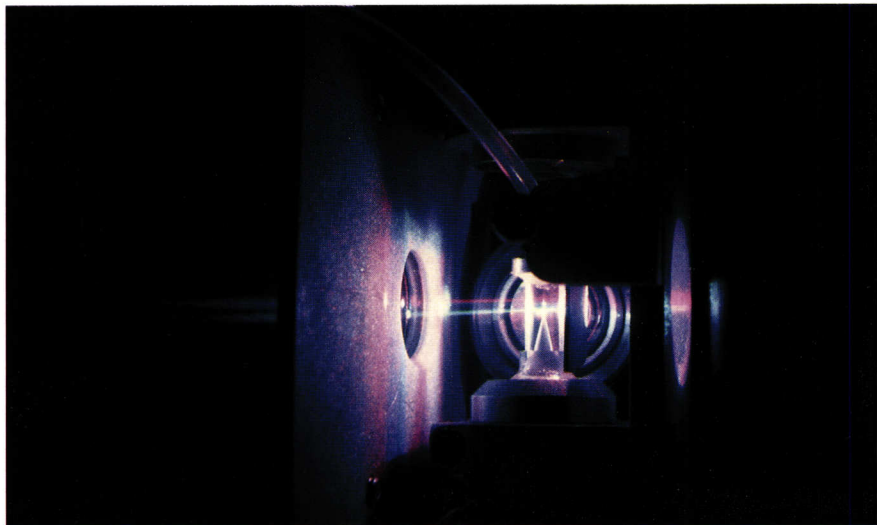
Several aspects of exposure of the skin to chemical compounds are being investigated. For most of the compounds that are used in industry or elsewhere, data on skin penetration are lacking. New models are being developed to enable the rapid

determination of the penetration capacity of chemical agents and to investigate the toxic actions of chemicals on the skin. Knowledge of skin penetration and skin toxicity is indispensable for the development of adequate measures to prevent local damage to the skin and systemic injuries elsewhere in the body. In addition, field studies are carried out to investigate possible health risks and health effects that are due to occupational exposure of the skin to industrial products.

A culture of human skin cells.



A flow cytometer is capable of separate analysis of approximately ten thousand particles per second. Laser beams pass through a suspension in a cuvette. The scattered light and the fluorescence intensity of each particle is measured with light-sensitive detectors. The RELACS III (Rijswijk Experimental Light Activated Cell Sorter) is shown.



Neurotoxicology

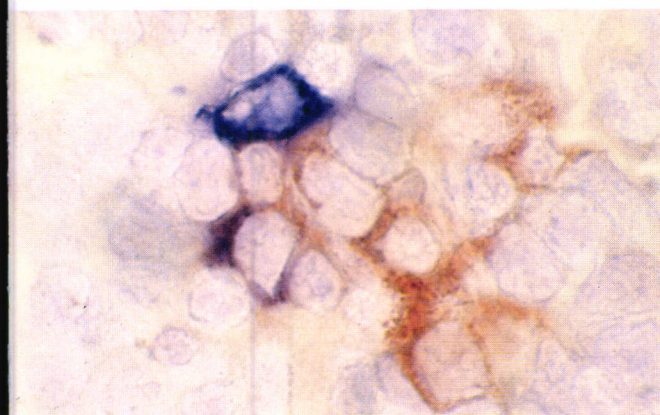
Damage to the nervous system as a result of exposure to chemicals may have serious physical and mental consequences. Therefore, an important objective of this research programme is to develop noninvasive diagnostic methods for the early detection of damage to the nervous system in humans. Animal studies are carried out to gain an understanding of the way in which such chemicals affect behaviour and neurochemical indicators. An experimental model using nonhuman primates is being developed to improve the evaluation and assessment of the possible adverse effects of therapeutic and other agents.

Biological monitoring

Occupational exposure to some chemicals can be determined by measuring the quantity of that compound or its metabolites in the blood, urine or exhaled air. However, these data are significant only if they can be interpreted in terms of a health risk. Research involves mainly the development of new methods for estimating such hazards and the improvement of existing ones.

Toxicological risk-evaluation

TNO Health Research has a supporting role in the toxicological evaluation of existing and new chemicals (under the Dutch Act on environmentally dangerous compounds) and in the toxicological evaluation of pesticides in the context of the relevant authorization regulations (covered by the Act on pesticides). In addition, toxicological evaluations are carried out for classification purposes and for the assessment of occupational exposure limits (TLV values).



Simultaneous staining of cells in a thin section of tissue. One antibody is linked to an enzyme alkaline phosphatase and stains the cells blue. The other antibody is linked to horseradish peroxidase and stains the cells red. If the two different determinants are expressed in one and the same cell an intermediate colour will result: violet.



Determination of the metabolite 2-thiothiazolidine-4-carboxylic acid (TTCA), a measure of exposure to CS₂ (carbon disulphide) in urine samples.

9 Medical-biological defence research

Pharmacological defence research is concentrated on treatment of victims of chemical warfare.

Unfortunately, chemical weapons have been used extensively in the past few years in Angola, the Middle East and South-east Asia. The organ systems most affected are the skin and the nervous system. Skin research is concentrated on quantifying penetration of and damage to the skin and the search for protective means. New methods are being investigated for the improvement of wound healing and skin grafting. The use of autologous skin cells grown in tissue cultures into thin skin films is being studied. Research is in progress to investigate whether this skin tissue can be used to improve the healing process in case of serious dermal injuries, such as burns.

The nervous system is the main target for nerve gases. Exposure to such gases may lead to acute respiratory paralysis. Effective therapeutic agents are available for most nerve gases. Research is devoted to the development of therapeutic and prophylactic agents for those gases for which no therapy is currently available.

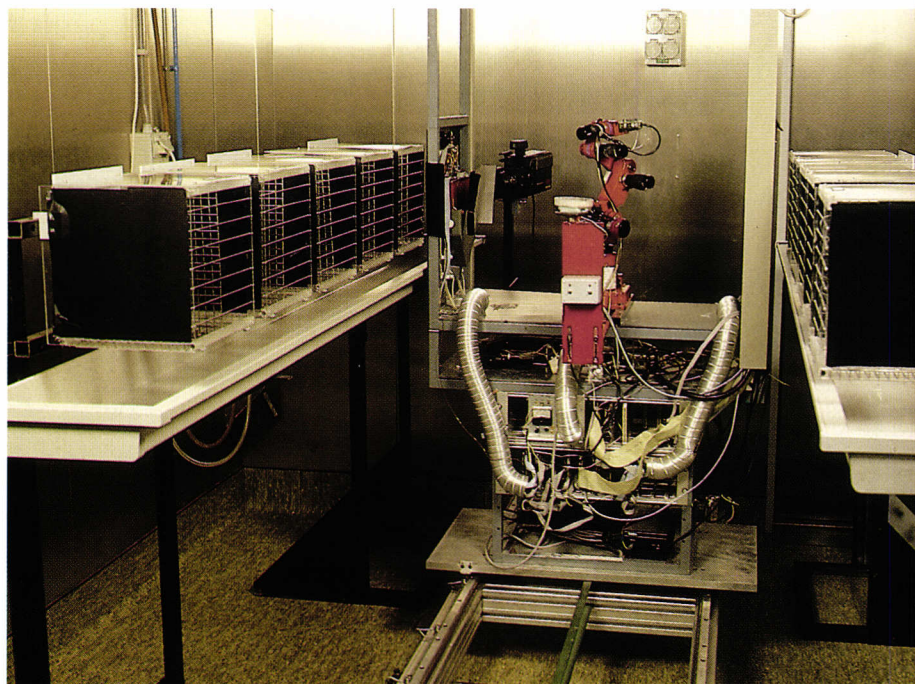
Unfortunately, some nerve gases have a very strong direct toxic effect and may also cause permanent

brain damage, even after treatment with the existing therapies. It is now being attempted to design a treatment that prevents or limits permanent damage.

Another major problem arises after a low level exposure to nerve gas. Animal studies have shown that exposure to low doses of nerve gas may have no effect on physical well-being and motor functions and may go unnoticed, but nevertheless may lead to changes in higher (cognitive) functions of the brain. This may have severe consequences for the human existence. Methods are being developed to determine the extent and severity of these cognitive changes.

In the context of medical-biological defence research, investigation are also being carried out on the development of a biological radiation dose meter that is capable of determining the level of radiation to which a victim was exposed from blood samples. Comparable studies focus on the biological dosimetry of exposure to mustard gas. With regard to biological agents TNO Health Research contributes to the early detection of pathogenic microorganisms and the nonspecific enhancement of immunological resistance to pathogens.

Robot-controlled marmoset set-up for measuring very low concentrations of nerve gases.



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In the area of occupational and environmental health, TNO Health Research studies those factors in the human environment that influence health and well-being. Human health and well-being can be influenced by biological agents (viruses, bacteria), chemicals (pesticides, solvents, metals etc.), stress and physical factors (radiation, sunlight, noise) in the indoor and the outdoor environment. Most research in this area concentrates on man in his work situation, with the objective of matching jobs with the requirements that can be set from the point of view of health, safety and well-being. This research is commissioned by the government, trade and industry (employers and employees) and organizations in the areas of occupational health care and Social Security.

Stress

The interest in the problems of stress in work situations is increasing. This is partly due to the large number of persons declared unfit for work because of psychological disorders and partly because stress affects the performance of workers and consequently the vitality of companies. Studies involve:

- developing methods to measure stress in the work situation;
- identifying risk groups in the working population;
- developing information programmes and practical methods to prevent stress in trade and industry.



Measuring the concentration of styrene in the air exhaled by workers in the polystyrene industry.

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Physical workload

Disorders of the locomotor system account for about 25 per cent of cases declared unfit for work. These afflictions may involve the back, neck, shoulders, elbows and/or wrists. Occupational factors that cause injuries include: heavy lifting, prolonged work in a slumped posture and/or working with the arms above shoulder level. To achieve effective prevention much research is still needed. Studies focus on:

- the epidemiology of factors that lead to complaints;
- ergonomic measures for diminishing the load;
- possibilities for information and training to prevent complaints;
- development of methods for early diagnosis to detect incipient health damage.

Chemical and biological aspects of working conditions

Research in occupational health care and industrial hygiene focuses on the significance and consequences of handling industrial chemicals for the health of the workers. TNO Health Research performs occupational health research directed at detection, evaluation and prevention of health hazards resulting from occupational exposure to dangerous chemicals. In addition, research is being done on health risks resulting from exposure to biological agents.

During the repair activities at the Hem Bridge in Amsterdam the exposure to lead was measured.



Man at work

In the category of 'man at work', research is being done on occupational health, epidemiology and ergonomics. In addition, socioscientific studies are being performed of health protection and improved performance of the person on the job. Topics of investigation are:

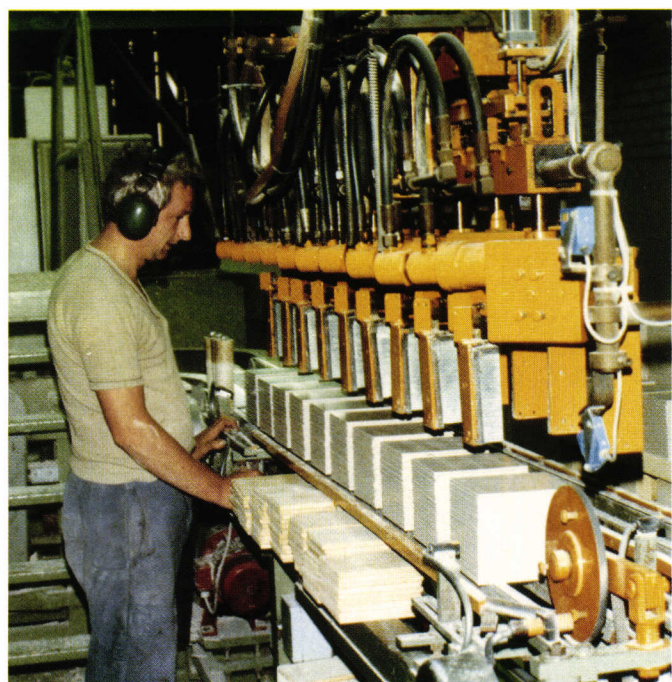
- epidemiological research on occupational diseases and accidents at work;
- physical work load and health problems of the locomotor system;
- psychic and psychosocial work load, stress;
- noise, hearing damage, noise annoyance;
- computerization and work;
- causes of sickness absenteeism and permanent incapacity for work;
- integration of disabled persons into the work process;
- quality of occupational health care;
- integrated audits of working places, companies and branches of trade and industry, concentrating on demanding working conditions, health problems

and possibilities for improvement. This is done in close cooperation with other TNO institutes that have specialized technical know-how.

As an extension of these activities TNO Health Research establishes courses to train occupational-health officers. Joint activities of TNO concerning working conditions are being coordinated by the TNO Expert Committee on Humanization of Work, a special committee (called HUMAR) which is part of the NIPG-TNO. This institute also houses the Office of the (former TNO) Occupational Health Research Committee (called CARGO), which advises the government on research on occupational health.



To prevent damage to the auditory system, hearing-protection equipment has been developed.



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Colophon

This brochure is a production of TNO Health Research.

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Cover

The new Gaubius Laboratory in Leyden against a
background of human liver cells

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TNO organisational structure



Supervisory Board

Board of Management - - - National Defence Research Council

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TNO Environmental and Energy Research

TNO Building and Construction Research

TNO Industrial Research

TNO Nutrition and Food Research

TNO Health Research

TNO Defence Research

TNO Policy Research

TNO Institute of Preventive Health Care
TNO Institute of Ageing and Vascular Research
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