CELL BIOPHYSICAL RESEARCH IN DEBRECEN

The Department of the Medical Physics of the Medical Faculty of Debrecen University was established in 1921. The first director of the Department was Prof. József Wodetzky, who besides the educational and research activities in medical physics, also established an observatory. From 1934 to 1968 Professors János Bodnár, Zoltán Gyulai, Sándor Szalai and Lajos Tóth followed him on the Department. The Medical Physics Department was reorganized and became Department of Biophysics in 1969. Since that time the Department is headed by Prof. Sándor Damjanovich. The Department is well equipped, according to European standards. The available instruments are: fluorescence activated cell sorter, patch-clamps, tissue culture facilities, equipment to measure rotational anisotropy, lateral diffusion (FRAP), fluorimeters, photometers, microscopes etc.

The main research field of the Department of Biophysics was the experimental and theoretical investigation of relationship between enzyme structure and function. They characterized the internal dynamics of model peptides and enzymes and found close correlation between the internal mobility of enzymes and their catalytic activity. Lately, the interaction of cell surface ligand binding sites and the mechanism of information transfer through the cell membrane is studied among other cell biophysical problems.

The primary target of external stimuli is the plasma membrane for cells of living organisms. These specific signals are transmitted via second messengers. Beside the well known biochemical mechanisms of ligand-receptor interaction there are numerous physical events involved such as the alteration of the cell surface which takes place at the receptor level. Signal transduction processes across the cytoplasmic membrane and the membrane itself both play an important role in cell proliferation and differentiation. The interaction between a hormone and its receptor is followed by biochemical processes (cyclic nucleotide, phosphoinositol cascade, cytosolic and membrane bound kinases, Ca^{2+} signal), by changes in physical parameters of the cell membrane (ion permeability, membrane potential, membrane fluidity), and by dynamic rearrangement in twodimensional patterns of cell surface constituents. The signal transduction process is in turn influenced by the actual stage of the ensuing proliferation.

Specific problems under investigation in our institutes are the following:

Major histocompatibility complex (MHC) class I molecules are glycosylated integral membrane proteins. Their main function is presentation of antigens to T lymphocytes through specific interactions between multiprotein complexes of the antigenpresenting cell surface and the TcR/CD3 complex of the T lymphocytes. These specific molecular interactions between the T-cell receptor and the peptide-MHC complex result in T cell activation initiating the immune response. The structurally distinct, but genetically related class II MHC molecules play a similar role in presentation of peptides derived mostly from exogenous proteins. Earlier results from our laboratory (Szöllősi, J., et al., J. Immunol., 1989, 143:208), in accordance with other findings, revealed an intimate relationship (close proximity on the cell surface) between class I and class II MHC molecules. This kind of association between class I and class II molecules may have functional significance through regulating peptide-binding properties of class I and/or by assuring the conditions for their concerted action during the immune response.

The Centre for Theoretical Medicine, Debrecen

Integrins are members of a large family of α β heterodimer cell surface molecules appearing on a wide scale of cells. They play key role in adhesion of cells to other cells and to the extracellular matrix. A member of this family is LFA-1 antigen involved in adhesion of T lymphocytes to activated endothelium, when it binds to the appropriate ligand of the partner cell, to the ICAM-1 protein. ICAM-1 is a 80–115 kDa glycoprotein, member of immunoglobulin (Ig) superfamily. The LFA-1/ICAM-1 connection is a good example of interaction between Ig and integrin superfamilies. Producion of monoclonal antibodies initiated mapping of ICAM-1 positive cells. While LFA-1 is expressed mostly on leukocytes, the ICAM-1 is found on a variety of other cells. These observations raise the question: How is ICAM-1 organized on the cell surface and what may be the role of its hetero-associations with MHC molecules in its function?

We have discovered a novel immunomodulatory effect of the triphenylmethane polymer aurintricarboxilic acid (ATA). This effect is based on a conformational change elicited by the drug in certain receptors. This effect parallels and may explain its antithrombotic effect which is meditated via the von Willebrandt factor. We plan to extend the investigations to the platelet surface receptors and to the ICAMs. The methodological basis of this approach is a novel technique developed by us (Szabo Jr. et al., 1992, Biophys. J. 61:661), based on the pFRET principle. Platelet-derived Growth Factor (PDGF)-induced cell signals have been implicated in the pathogenesis of human brain tumors of mesenchymal origin. An analysis of this signaling system may help us to understand the pathophysiology of the tumor and may lead to its rational treatment. We found that PDGF-induced calcium signaling depends upon cell confluence in human brain tumor cell culture system. (Szöllősi, J., et al., Cytometry, 1991, 12:707; Szöllősi, J., et al., Cell Calcium, 1991, 12:447; Feuerstein, B. G., et al., Cancer Res., 1992, 52:6782). Thus, we must ask how cell confluence affects PDGF-induced cell signaling. This inquiry would help us to better define the PDGF-induced signaling system in brain tumors and to understand how the system functions in different environments. Our starting point is the question whether cell-to-cell communication is a parameter in the problem. It seems rational that alterations in direct cell contact should affect cell-to-cell communication. The parameters that we choose to examine here are gapjunctions, cell surface dynamics and ion channels. Since we have observed alterations in calcium signaling that depend upon cell confluence, now we are going to concentrate on the beginning and the end of the PDGF-signaling pathway, and on the calcium signal itself. At the beginning of the pathway, we ask whether confluence affects the PDGF receptor and its activation. At the end of the pathway, we examine how our model brain tumor cell line in various stages of confluence synthesizes DNA in response to PDGF. Regarding the calcium signal itself, we ask whether various parts of calcium signal are affected by changes in confluence.

Sodium channels are extremely important in excitable cells, however much less is known about their involvement in cell activation processes.

It has been shown that an almost ubiquitous Na^+ influx was triggered by a particular ligand, bretylium tosylate (BT) activating the Na^+ -K^+ -ATPase and repolarizing the plasma membrane. Recently, the repolarizing action of BT has been verified by patch-clamp. The well known anti-arrhythmic effects of BT could be attributed to repolarization, too. It has been postulated on the basis of experimental observations, that the above effect of BT may influence the alternative cell activation processes in lymphocytes, the one involving the phosphatidyl-inositol-diphosphate cascade and activating the protein kinase C, and the other working via IL-2 signaling. It has been suggested, that those signal transducing processes, which are more exposed to membrane potential changes of the plasma membrane are more sensitive to BT. The detailed mechanism of the differential action of BT on the two separate signal transducing pathways is still to be clarified by patch-clamp experiments on lymphocytes (Gáspár et al.BBA 1137:143–147 1992).

The involvement of classic voltage-dependent Ca^{2+} channels has been assumed in cell activation processes, because the T-cell receptor/CD_3 ligands or mitogenic lectins induce an increase in intracellular Ca^{2+}. It has been suggested that the step that requires Ca^{2+} in mitogenesis is the production of IL-2, therefore – although Ca^{2+} channels/transporters appear to play an important role in mitogene induced IL-2 proliferation, – Ca^{2+} -independent modes of signal transduction are also present in the T-cell.

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ZOLTÁN KRASZNAI
Assistant Professor

DEPARTMENT OF BIOPHYSICS, UNIVERSITY MEDICAL SCHOOL OF PÉCS

The legal predecessor of the Department was the Chair of Physics of The Hungarian Royal „Erzsébet" University that had been moved from Pozsony (now Bratislava) to Pécs after the Great War in 1921. Professor of physics László Rhorer was the director of the Department over the period of 1923 to 1936. He was interested in the fields of physics related to biomedical problems. He made an outstanding research investigating the kidney function, medical radiology and the medical application of X-rays. His death interrupted the promising development. His successor (Elemér Császár 1937–1944) focused his attention to the physics of X-ray and its medical application.

The Chair of Medical Physics began to develop and became a true centre of biophysical research during the decades after the Second Word War. Eugene Ernst (1895–1981) was appointed to the director of the Department in 1945 and he directed it for 27 years. (1945–1972). He played a definitive role not only in the development of the Department but in creating real biophysics at national and international level and he achieved a general appreciation of this new branch of biosciences.

He proposed to declare officially that the chair was a „Department of Biophysics", the first one that became the birthplace of the biophysical research and education in Hungary. The first national „isotope laboratory" of biological profile was established in the Department in 1954. Eugene Ernst's initiation was to form the „Research Group at the Department of Biophysics of the Hungarian Academy of Sciences" that became the basis of the development of the Hungarian biophysics. This Researh Group works within the Department since it has been founded. Eugene Ernst organized the Hungarian Biophysical Society in 1961. He was its first President and then its honorary life President (1969–1981). He had a significant part in organizing the International Union for Pure and Applied Biophysics (IUPAB) in 1961, he was a member of the IUPAB Council over two periods. He proposed to publish the journal „Acta Biochimica et Biophysica" of the Hungarian Academy of Sciences (1966), he was its first Editor in Chief. This Journal gave the Hungarian biophysicists a possibility of publication over two decades. Professor Joseph Tigyi was the following director of the Department (1971–1991). He carried on to develop the activity of the Department on the basis of its traditions.

Under his directorship the Department moved from its former, very modest conditions to a detached building in the new University Campus as a result of his organizing activity. He established international co-operation with quite a few well-known research laboratories abroad, e.g. the Biophysical Department of the Humboldt University of Berlin (Prof. R. Glaser), the Department for X-ray investigations of solids (Academy of Sciences of Austria, Graz, Prof. Laggner), the Biophysical Institute of Pushchino (Prof. G. Frank), Department of Psychobiology at the University of California, Irvine (Prof. M. Miledi). He was engaged in organizing scientific life as the President of the Biological Section of the Academy, President of the Hungarian Biophysical Society, Vice President of the Academy, Editor in Chief of the Acta Biochimica et Biophysica and at last but not least as the Secretary General of the IUPAB. All of these activities made a significant contribution to the development of the national and international biophysics. The present director of the department is Prof. Béla Somogyi from 1992. He is interested in the investigation of problems of the molecular biology by luminescence spectroscopy. He established a new laboratory in the department equipped to do experiments in fluorescence spectroscopy.

The fields of research done in the Department were determined partly by national traditions partly by the ambition to cover a possibly wide spectrum of the research in Hungary. That was an important point and a significant drive because the Department was the only laboratory that investigated biophysical problems in Hungary for a long while.

The traditional subjects of the department can be classified, as follows:

1.) Structure and function of muscle
2.) Problems of excitatory processes in muscle and nerve
3.) Biological effects of ionizing radiations
4.) Transport of liquids and the state of water in biological systems.

The investigation of the structure and function of the cross striated muscle was the most important research in the Department for a long while. The significant new results of this research were the followings:

– Detection of structural changes and rearrangement of substances during muscle activity (electron microscopy and micro-autoradiography)

– Analysis of the time dependence of shortening of muscle

– Efficiency of muscle work

– Volume decrease.

Eugene Ernst's comprehensive monograph (German version 1958, English version, updated 1963) analyses the results of these investigations. This book considers some significant results of other fields of investigation, too:

– An alteration of the potassium-sodium exchange occurs under the effect of direct stimulation by electric current and under the effect of stimulation through nerve (physiological, indirect stimulation)

– Trace elements have a significant effect on the electrical properties of excitable tissues.

The investigation of the interaction of local anaesthetics with nerve membranes (in progress now) is an important contribution to the interpretation of the basic excitatory phenomena.

– Small doses of ionizing radiations may result in excitation of muscle tissues, contrary to the former opinion that these radiations have no effect on muscle.

– Visible light and UV radiation have excitatory effect on sensitized nerves and muscles.

– Temperature gradient produces a thermo-electromotive force in muscles and nerves.

– Trace elements of extreme low concentrations have a crucial influence on the response of biological tissues to radiations in analogy with impurities in semiconductors.

– Biological significance and role of thermodiffusion and thermo-osmosis were investigated in connection with the research about mobilization of water in biological tissues.

The Department had an initiative role in developing the teaching of biophysics as witnessed by Eugene Ernst's textbooks „Introduction to Biophysics (1947; revised and updated edition 1966) and the „Biophysics" written by many contributors, editor: Eugene Ernst (1974, 1977).

More information: Dr. Béla Somogyi (Department of Biophysics University Medical School of Pécs P. O. Box 99. 7643 Pécs, Hungary)

BÉLA SOMOGYI
Director

INSTITUTE OF BIOPHYSICS, SEMMELWEIS UNIVERSITY OF MEDICINE AND RESEARCH LABORATORY FOR BIOPHYSICS, HUNGARIAN ACADEMY OF SCIENCES, BUDAPEST

The two institutions exist together in the same place, the Research Laboratory is a transferred unit of the Academy into the University Institute. The University Institute was established in 1949 while the Laboratory in 1980. The great majority of the staff (18) belongs to the University (while two others to the Academy) performing the teaching duties on three faculties of the University (Faculty of General Medicine, Pharmacy and Dentistry). There are lectures and practicals from biophysics (partly in German and English for the roughly 300 foreign students) every year in both semesters for altogether 900 students. Besides the weekly lectures and practicals exams (semifinals nad finals), entrance examinations, non obligatory courses, optional parallel lectures etc. mean the teaching activity of the staff.

At the same time research work is done by the members of the Institute (Laboratory) which is supported partly by the Academy of Sciences, but mostly by different grants and international R&D programs.

Main fields of interest: Structural studies on biological macromolecular systems (virus nucleoproteins, proteins, membranes); investigation of the molecular mechanism of structural and functional changes exerted in biopolymers by different physical and chemical agents.

Macromolecular systems studied:

Nucleoproteins: bacteriophages (chromosome models) T7, MS2; of high purity and concentration (100 mg/ml), their isolated DNA/RNA components.

Proteins: monomeric hemoproteins as myoglobin, hemoglobins, cytochromes, peroxidases.

Membranes: biological (red blood cell membrane), artificial (bimolecular lipid membrane-peptide complex).

Techniques: UV-visible absorption, fluorescence and phosphorescence spectroscopy, luminescence lifetime measurements, polarized emission studies, laser excited fluorescence spectroscopy at cryogenic temperatures: fluorescence line narrowing, dynamic light scattering; microcalorimetry, automatic apparatus for measuring the parameters of phage-bacterium interaction, halfautomatic apparatus for measuring the parameter of bacterial growth; measurements of biological solar dosimetry (direct and global exposure), underwater biological dosimetry radioisotope labelling (used as daily routine in kinetic studies).

Current topics of interest and ongoing projects

1. Investigation of the structure of macromolecular systems.

Nucleoproteins: Kinetics and structural changes in T7-phages induced by different solvents, quantitative characterization of dark genotoxicity and photoreactivity of coumarin derivatives where the structural and functional changes are studied on nucleoprotein complexes.

Proteins: Optical monitoring of the structure of proteins, e.g. monitoring the protein structure through the phosphorescence of tryptophan, luminescent labelling of liposome-protein systems in order to study the drug-binding effects, molecular basis of PUVA therapy: binding of porphyrins to proteins.

Membranes: Experimental and theoretical investigation of the structure of simple membranes, as well as the phase transition temperature and enthalpy as indicator of functional changes under the effect of channel forming peptides and tenzides.

2. Environmental biophysics

Investigation of the action mechanisms of ultraviolet radiation, as well as some chemicals and drugs as factors influencing the state of biosphere, the estimation of their biological dose and prediction of their health hazards.

Bacteriophage T7 (in solution) and uracil crystalline thin layer biological sensors with portable measuring instruments have been developed and used. These sensors are uniquely suitable for evaluation and prediction of health risk of UV-B radiation.

Two different prototypes of microbiological automatic measuring apparatus were developed which permit (a) exact and short term determination of the genotoxic and cellular toxic effects of a wide variety of substances, and (b) very sensitive determination of the concentration of antibiotics used in animal foods and food premixes.

GYÖRGYI RONTÓ
Director

The opening ceremony of the 12th National Meeting, Budapest, 1983.
(From right: Prof. I. Tarján, the previous director and Prof. Györgyi Rontó the present director of the Institute.)

DEPARTMENT OF BIOPHYSICS, JÓZSEF ATTILA UNIVERSITY SZEGED

Biophysics teaching in Szeged started in 1966. The Institute began its activity in 1969 originally in symbiosis with the Institute of Experimental Physics and in 1976 it became an independent unit of the Faculty of Sciences located at its present place. The founder and head of the Institute until 1991 was dr. L. Szalay. The late sixties were favorable for biophysics in Szeged, the Biological Research Center of the Hungarian Academy of Sciences was established, teaching and research in modern biology started to emerge.

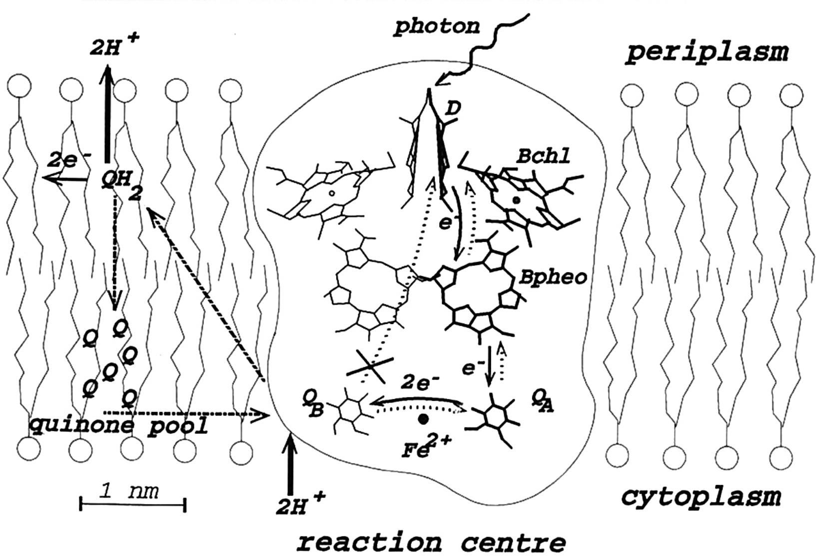
The Department of Biophysics grew out of the Department of Experimental Physics and this determined our early research program based upon the experience and facilities available: from the luminescence properties of organic dyes to the optical spectroscopy of proteins, photosynthetic pigments and micellar systems. Cooperations on national and international level turned our interest from these model studies to physiological investigations on green plants and algae. All the experiences on applications of luminescence in biology and medicine were collected in a handbook, as a joint work with the Biophysics Institute of the Kossuth Lajos University, Debrecen in 1983.

Since 1966 our main task has been teaching students of biology, of teachers in biology and also medical students of Szent-Györgyi Albert Medical University, Szeged. The main activities of our educational duties are: lecturing, laboratory practices, introducing students into research work. Our experiences in this field was collected in a textbook, titled Biophysics (published by the Ministry of Public Education in 1985 and 1986), and more recently in a manuscript of a scheduled textbook, titled Introduction to Biophysics. Since 1985 we have been participating in the program of teaching foreign students of medicine in English.

From 1972 a smaller group sponsored by the Hungarian Academy of Sciences had worked in the Institute and became independent in 1990. The main interest of this group was herbicide resistance of plants.

The Institute had and still has wide international relations. Our coworkers spent long periods in many laboratories and contributed to their work in Urbana, Baltimore, Bethesda, Rochester, Gif-Sur-Yvette, Göttingen, Tübingen, Manchester, London. These cooperations enriched our research program. In 1991 dr. Péter Maróti became the head of the Institute (further information: Egyetem u. 2. Szeged, Hungary, H-6722).

Nowadays the major interest is the study of primary photophysical and photochemical events of photosynthesis in bacteria and single-cell algae. Light induced electron transfer generates a transmembrane proton gradient and, ultimately, ATP. This complex system is studied by biophysical and biochemical techniques and the photochemical processes are followed by optical kinetic methods. We are seeking a description of the structural relationship between the reaction centers, proteins, quinones, and the functional interaction between the electron transfer and proton turnover (binding, unbinding). In



photon
periplasm
2H+
2e-
QH2
D
Bchl
e-
Bpheo
Q
Q
Q
Q
Q
Q
e-
2e-
QB
QA
quinone pool
Fe2+
1 nm
2H+
cytoplasm
reaction centre

other aspect we are investigating the role of the membrane to determine the electron and proton transfer reactions. The close similarity between the reaction center of bacteria and PS2 of higher plants enables us to propose mechanism for the action of commercially important herbicides. Kinetic spectroscopies have shown that the reaction center (see Fig.) exists in more conformational substates which are in equilibrium. The observed kinetics and stoichiometry of flash-induced proton binding to the reaction center depend on the conformational changes of the protein by controlling the protonatable amino acid groups.

Within the frame of international cooperations some colleagues of ours became interested in problems falling out of our research field being just methodically near to it. One of them dealt with the study of the photosynthesis of cyanobacteria in the Imperial College of Sciences, Technology and Medicine (London). This problem was studied mainly in the direction of photoinhibition by equilibrium and kinetic measurements of fluorescence and oxygen evolution. Another coworker studied the dynamical properties of lymphocyte membranes in the USUHS Pathological Institute (Bethesda, MI) by means of flow cytometry and laser microscopy. A common work was done in the Biochemical and Molecular Biology Institute of the MAYO Foundation (Rochester, MN) related to the study of the directional changes of myosin molecules in muscles. Measurements of fluorescence polarization spectra of labelled molecules were carried out to clear up the movement of cross bridges as a function of physiological states.

The members of the Institute are as follows:

Head of the Institute: Prof. P. Maróti
Scientific adviser: Prof. L. Szalay

Teaching and research staff:

E. Bálint
L. Kálmán
G. Laczkó
L. Nagy
A. Ringler
J. Tandori
Cs. Tápai
K. Turzó
Z. Várkonyi

Technical staff:

Mrs. M. Bánáthy
K. Csontos
Mrs. I. Dunai
Mrs. A. Eperjesi
A. Jedlicska
Mrs. M. Kothencz
Mrs. J. Laskay

ZOLTÁN VÁRKONYI and LÁSZLÓ SZALAY

INSTITUTE OF BIOPHYSICS, BIOLOGICAL RESEARCH CENTRE OF THE HUNGARIAN ACADEMY OF SCIENCES

According to the interdisciplinary character of biophysics, the research work of the Institute is related to a large scale of physical aspects of biological phenomena. The laboratories are well-equipped, and most of the major items of biophysical equipment are available. They include electron microscopes, ESP instruments, spectrophotometers for UV to IR absorption measurements, fluorimeters, laser-Raman and CD spectrometers, atomic absorption spectrometer and various chromatographic facilities. The home-made, fast kinetic setups are important representatives of our equipment: laser flash -induced absorption kinetic changes can be measured with 10 ns time resolution.

The four independent research groups are organized according to the level of complexity of the biological material investigated.

1. Laboratory for membrane bioenergetics (Lajos Keszthelyi)

The central interest of the research group is connected to the elucidation of the molecular mechanism of energy transducing proteins.

Molecular motions and charge translocations coupled to the protein function are investigated with specroscopic methods of high time resolution. A novel method has been developed in our laboratory for the quantitative characterization of fast, intramolecular charge displacements. Application of this powerful method yielded important new results in the interpretation of the bacteriorhodopsin proton pump, and it was successfully used in the investigation of other proteins, e.g. the visual pigment of algea, or the Na^+K^+–ATPase, as well.

2. Laboratory of molecular dynamics in membranes (László Horváth)

The aim of this research unit is to study the molecular dynamics of lipids at the interface of membrane proteins, and to characterize membrane-bound enzymes.

Spin label electron spin resonance (ESR) spectroscopy has an optimal sensitivity for distinguishing bulk fluid lipids and motionally restricted solvation lipids because of its optimal time scale. Microscopic and macroscopic lateral diffusion are followed by molecular collision and imaging experiments, respectively.

In addition to the lipid research, membrane-bound proteins and membrane-coupled processes are also investigated:

– redox systems in the plasma membrane of mammalian, bacterial and yeast cells;

– photosynthetic systems, protein-pigment complexes by spectroscopic methods;

– membrane-bound hydrogenase enzymes with special emphasis on solar energy bioconversion.

3. Laboratory of stress physiology and transport in plants (László Erdei)

The laboratory investigates mechanisms of stress tolerance and adaptation in plants. The work is based on wide experiendce obtained in studying the regulation of transport processes and the principles of optimalized nutrition in plants. The recent work is focused on the following main topics:

– the mechanisms of salt and drought tolerance at different levels of organization;

– pollution stress tolerance and stress-induced substances;

– calcium-calmodulin related mechanisms.

The role of growth regulators and calcium in stress responses and adaptation are also investigated.

4. Laboratory of molecular neurobiology (Ferenc Joó)

Interactive mechanisms providing the molecular basis of plastic neuronal reactions in the peripheral and central nervous systems have been studied in this laboratory using an interdisciplinary approach in several model systems of different complexity.

By using rapid freezing and freeze-fraction techniques, we were able to follow the morphological changes in nerve terminals with high time resolution.

Other studies were designed in order to elucidate the significance of certain particular morphological units in the formation and maintenance of the regular structural and functional integrity of the main olfactory bulb.

Biological Research Centre of the Hungarian Academy of Sciences, Szeged

Special emphasis is given to search for the recognition of new principles which could promote regenerative efforts of the central nervous system after different injuries, such as brain ischemia and edema.

LAJOS KESZTHELYI and PÁL ORMOS
Director Deputy Director

THE „FREDERIC JOLIOT-CURIE" NATIONAL RESEARCH INSTITUTE FOR RADIOBIOLOGY AND RADIOHYGIENE (OSSKI)

The establishment of an institute for radiobiology research was decided by the government in 1954, immediately after the Bikini-test, the radioactive debris of which resulted in a global contamination and worldwide concern. The actual foundation, however, took place on 1 January 1957. The task of the institute was expanded in the subsequent years to radiation hygiene, development of radiopharmaceuticals and other products labelled with radionuclides, and control of equipments emitting non-ionizing radiations.

At present, the institute is made up of three departments. These are radiobiology research, radiation hygiene, and radiation and radioisotope applications. There is also a division of non-ionizing radiations which is not attached to any of these departments: plus units covering central services, and economy and finance. The governing of the institute is assisted by a directorial council and an advisory board of external scientists. The institute is part of the National Public Health Centre, directed by the Chief Medical Officer and subordinated to the Minister of Health an Social Welfare.

Intensive research is performed in the Institute to study the mechanism of action of ionizing radiations in biological systems, with special emphasis to te following.

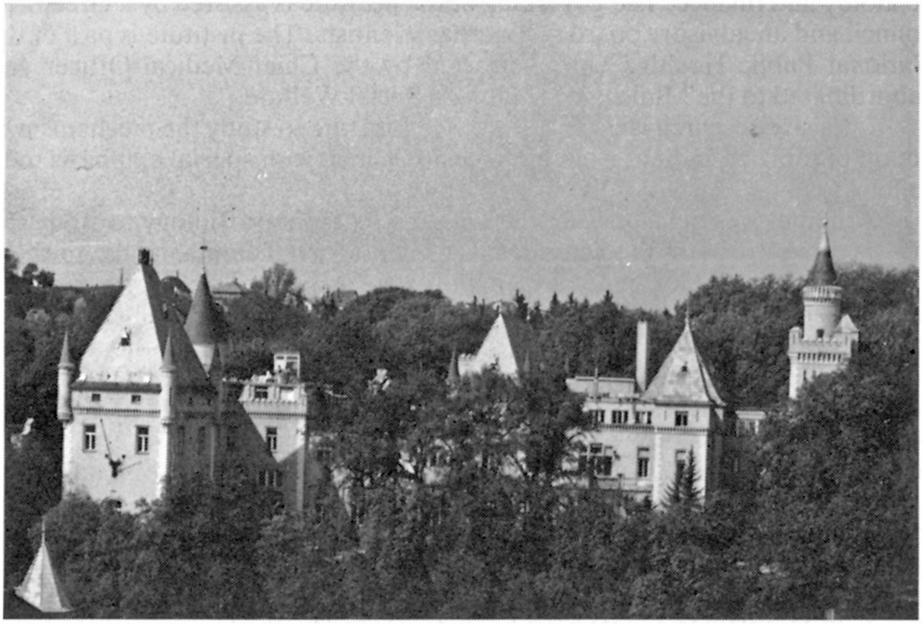
A model was developed in the Division of Tumour Biology to study the effects of neutrons on the health of offsprings of irradiated animals. In these experiments, pregnant mice were exposed to fission neutrons of a research reactor. The experiments demonstrated cellular death in the developing mouse foetus within 6 hrs, and 30–40% loss in the brain weights of newborn mice at about 3 weeks following irradiation with a dose of only 0.5 Gy. The results support the assumption that neuroblast proliferation is a highly radiosensitive process and its disturbance can explain the occurrence of severe mental retardation among the A-bomb survivors irradiated in utero during the 8th to 15th weeks of gestation. It was also observed that there was a higher than 60% incidence of neoplasms in 2 yrs old mice exposed to fission neutrons in the late gestation period compared with the normal incidence of about 20% in the unirradiated, control animals.

New complexing agents have been developed by the Division of Radiotoxicology to increase the elimination of radioactive strontium and cerium from the body, when these isotopes are already absorbed from the gastrointestinalt-ract or the respiratory system. These compounds are water soluble and of very low toxicity. A single injection of the new decorporating agents is capable to reduce the radioactivity content to 5–15% of the initial body burden. Based on these encouraging results, the drugs seem to be promising for the removal of internal radiostrontium contamination from humans.

Upon the initiative of the OSSKI there have been several remarkable achievements in the practical application of radiobiological effects and radioactive isotopes.

Among these, it should be mentioned that the introduction of radiation sterilization of disposable medical equipment and supplies in the country has been facilitated by the elaboration of the technology, by the establishment of a reliable sterilizing dose, and by the development of sterility control in the Division of Radiation Microbiology. The unit is an IAEA recognized training centre in radiomicrobiology for young scientists from the developing countries.

Radiation can also be used for detoxification of bacterial endotoxins, the most powerful immunomodulators. However, parenteral administration of native endotoxin is associated with severe, and mostly intolerable toxic effects. Irradiation of endotoxin with high doses (of the order of 150 kGy) decreases its toxicity without significant alteration of its immunogenic properties. Current clinical trials suggest that radio-detoxified endotoxin (TOLERIN^{R}) might be a useful tool in human medicine to enhance nonspecific resistance and to regenerate the immune system.



National Research Institute for Radiobiology and Radiohygiene, Budapest

Research, development and production of radioactive diagnostic agents for medical use have been performed in the OSSKI since the mid 60s. Until now about 10 different radiopharmaceuticals have been developed by the Division of Isotope Application for early detection of cardiac diseases, lung embolism, brain defects and lymph node involvements in cancer. In addition, various radioimmunoassay (RIA) kits have also been produced for detection of miniscule concentrations of biologically important substances, such as hormones, proteins, and drugs. Besides their use within this country, the products are exported to 18 countries in Europe, South-America and the Far East.

Besides the chromosome aberration analysis, the lymphocyte micronucleus test has been introduced for dose assessment in the case of radiation accidents. This method has proved to be a reliable and easily performable technique for screening of persons exposed to radiation in excess of about 0.2 Gy.

The Department of Radiation Hygiene consists of five divisions: operational and environmental radiation hygiene, personnel and environmental dosimetry, and a division of internal dosimetry and computer assisted radioactivity measurements.

The major task of the Division of Operational Radiation Hygiene is to provide expert advices and technical assistance for the National Public Health Authority in respect of complience of medical, industrial, agricultural, research and training places of work when using radiation sources with the applicable rules and regulations of radiation protection.

The Division of Personnel Dosimetry is responsible for the implementation of a centralized and nationwide dosimetry control of all individuals who are regularly exposed to ionizing radiation in their occupations. Radiation doses received from external sources by more than 15 thousand workers are monitored, evaluated and registered bimonthly by the Division using film-badge dosimeters.

The Division of Environmental Radiation Hygiene carries out radioactivity measurements in samples collected from various media of the environment including the atmosphere, surface and ground waters, soil, plant and animal organisms. A retrospective study on the radiostrontium contamination of the Hungarian population has also been performed by this unit through determination of ^{90}Sr content in more than 12 thousand teeth estracted on the bases of medical indications by the district dentistries of Budapest in the years of 1978–1992. In addition, the Division is the central organ of the nationwide Radiological Measurement and Data Acquisition Network of the Public Health Authority.

Site-specific levels of environmental radiation outdoors and indoors have been measured by the Division of Environmental Dosimetry since the early 1980s. Alterations in the dose-rates have been detected as a result of the actual meteorological conditions or as a consequence of the environmental contamination with radioactive substances after the accident at the Chernobyl nuclear power plant.

Individual monitoring of workers for internal exposure to incorporated radionuclides is not included in the program of the personnel dosimetry service. Thyroid activities of workers involved in the preparation of iodinated radiopharmaceuticals are, however, routinely checked by the Division of internal dosimetry and computer assisted radioactivity measurements, using a Canberra Body Burden Analysis System. The same system was extensively used after the Chernobyl accident for the measurements of gammaemitting radionuclides in the bodies of several hundreds of individuals, both Hungarian citizens and visitors of the country. Alpha-, beta- and gamma-spectrum analyses are also made by the Division in various environmental, food, water and other samples. In addition, data submitted by the operating organization as well as by the competent national authorities as the results of their environmental surveillance around the Paks Nuclear Power Plant are collected, evaluated and interpreted by the computer assisted Data Evaluation Centre operated by the Division.

LÁSZLÓ B. SZTANYIK
Director

BIOPHYSICS IN THE KFKI RESEARCH INSTITUTE FOR PARTICLE AND NUCLEAR PHYSICS OF THE HUNGARIAN ACADEMY OF SCIENCES

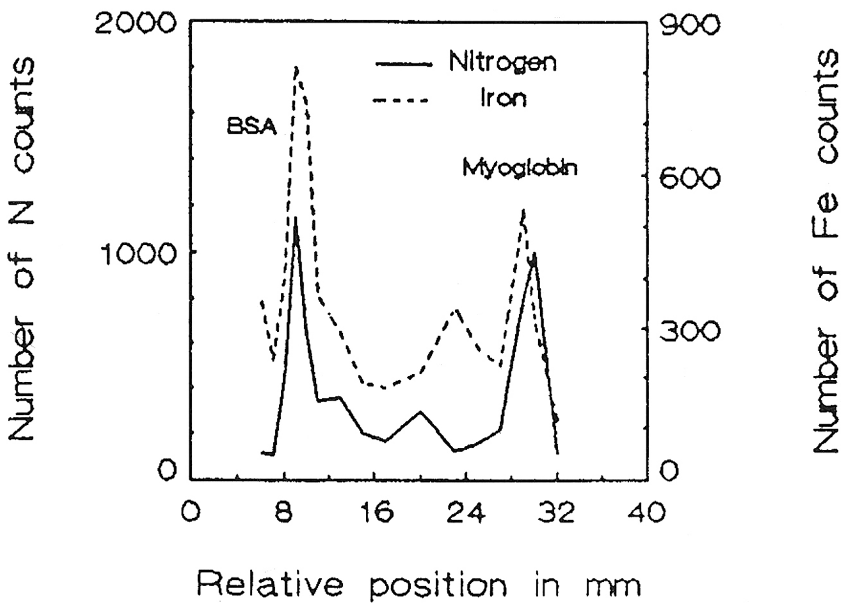
Research in relation to biological topics can be dated back to the early 1970s when Prof. Lajos Keszthelyi and his team of experimental nuclear physicists studied the origin of the optical purity of living matter by measuring time spectra of positron annihilation in several L- and D-amino acid samples. After these pilot studies the group officially became the Biophysics Group with the well-defined aim of applying atomic and nuclear techniques in solving certain biological/biophysical problems. Trace analysis of biological and biochemical samples utilizing ion beams of a few MeV energy offered the most natural way of making use of the scientific expertise and experimental instruments accumulated earlier. As the basic analytical tool the particle induced X-ray emission (PIXE) spectrometry, which is a rapid, sensitive, multielemental technique for elements heavier than Mg, was chosen, whereas special isotope sensitive nuclear reactions (NRA method) are used to detect lighter elements. Our new approach of using PIXE and suitable nuclear reactions simultaneously (PIXE-RP technique) has offered a unique tool to perform such kind of trace element analyses. The determination of trace element composition of various types of synaptic vesicles or the simultaneous measurement of the protein and metal ion content of a SOD enzyme are illustrative examples. Even more specific results can be obtained when the ion beam analysis is combined with biochemical separation processes. Developing a unique technique for direct in situ ion beam analysis of protein bands of thin layer electrophoretograms (PAGE, CAE) important new results in enzymology were obtained. It was found, among others, that the active center of the bacterial hydrogenase enzyme from Thiocapsa roseopersicina could contain both Fe and Ni ions and the Fe/Ni ratio was also determined. In contrast to former expectations it was also found that the Fe ions were bound to the larger subunit, whereas the smaller subunit carried the Ni ions following the drastic decomposing SDS-PAGE treatment.

Besides these analytical studies a second, more biological, biophysical oriented activity has gradually evolved. Valuable results were obtained from studying the biophysics of neuromembranes. The photocycle and the accompanying electric signals from bacteriorhodopsin (bR) were studied in different conditions by flashes from a nitrogen laser driven dye laser. The kinetics of spectral changes associated to solubilization and dark adaptation in native and solubilized Bacteriorhodopsin (bR) has been studied. For the experimental study of the activity pattern of neural cell cultures a multi microelectrode culture chamber system was constructed for monitoring simultaneously the morphological and electrophysiological development of neural cells in vitro.

The Biophysics Group commenced research into neuroscience as early as 1983. That time our research philosophy was motivated by the question, how can our knowledge on brain structure and function be utilized to design the near generation of computing devices? Later specific self-organizing algorithms were developed for understanding of certain fundamental neural phenomena, such as ontogenetic neural development, plastic behaviour and learning, periodic and aperiodic neural dynamics associated with neurological disorders, sensory motor coordination, different levels of vision, olfaction, dynamic memory organization etc.

Recently our research on theoretical and computational neuroscience mainly concentrated on making realistic neural models in terms of dynamic system theory. The mechanism of information processing in the olfactory bulb is studied by mathematical models. This neural structure, as well and its model, shows a set of dynamic phenomena, as oscillation, chaos, learning-induced bifurcation, coexistence of limit cycle and strange attractor, associative memory based on spatiotemporal patterns. An algorithm was established within the framework of Ventriglia's kinetic model to describe the activity circulation in the cortex – hippocampus – cortex loop. Some mathematical conditions of processing time-dependent inputs in neurodynamic systems were investigated. The conceptual power and the mathematical machinery of the notion of „computation with attractors" can be preserved for rather narrow class of the input functions only.

Just recently our theoretical activity was widened by bio-optical investigations. A general geometric optical method was presented to calculate the shape of the aspherical interface that eliminates spherical aberration of the doublet corneal lenses of some extinct trilobites. The aerial visual field of aquatic and amphibious animals distorted by refraction at the air-water interface was geometric optically investigated.



Fe and N distributions along a stained CA electrophoretogram containing myoglobin and BSA band measured simultaneously by PIXE and (p, p' γ) nuclear reaction.

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ZOLTÁN SZŐKEFALVI-NAGY
Head of the Biophysics Group

BIOPHYSICS IN THE DEPARTMENT OF ATOMIC PHYSICS, EÖTVÖS UNIVERSITY, BUDAPEST

Members of the Department are interested in a wide range of science from the quarks to the galaxies, including various biological fields. There is a theoretical, a nuclear, a resonance, and a biophysical group in the Department.

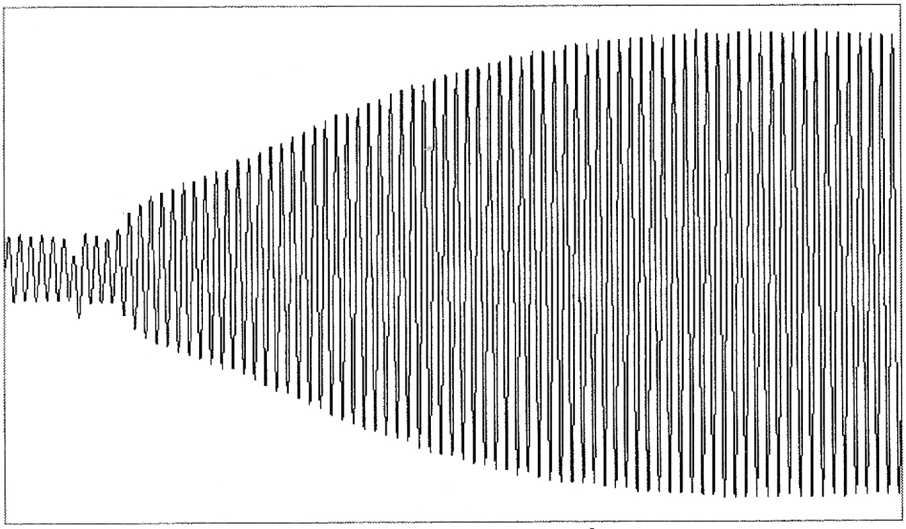
The Biophysics Group was founded in 1976. It is led by Elemér Papp, it's members are András Balázs, György Fricsovszky, Géza Meszéna and, temporarily, Ha Viet Hien from Vietnam.

A biophysics university course was launched in 1976. It was a subcourse of Physics from the 5th semester, and included biochemistry, genetics and physiology. In the last few years a reorganization was implemented in the physics course by introducing specialization from the 7 th semester. The biophysics course was reshaped to fit into this structure and a new type of biophysics lectures was started.

The central research topics of the Biophysics Group is bioenergetics: bacteriorhodopsin and photosynthesis. These works are carried out in close cooperation with the Biological Research Center in Szeged. In the early years orientation studies were our topics. Later the group shifted to electrical measurements.

E. Papp, Gy. Fricsovszky and Ha Viet Hien are involved in purple membrane research. Orientation of purple membranes in AC electric fields and the kinetics of the M state of the bacteriorhodopsin were investigated. In a new project transient conductivity change of the purple membrane suspension due to proton release and uptake is under investigation. (See the graph.) Three exponential components of the conductivity change were discovered.

Géza Meszéna in interested in photosynthesis research. In his first study, magnetic orientation of chloroplasts was investigated. Later wavelength-dependence of photovoltage of chloroplast suspension was discovered. Polarity of the photovoltage signal is opposite to expected in the long wavelength-side of the chlorophyll absorption bands. This phenomenon is explained in the term of the interference pattern of light distribution in the thylakoid membrane. He is also active in theoretical investigation of bioenergetic processes and the biological evolution.



András Balázs is interested in quantum biophysics of proteins. Together with other quantum chemists of our University, they calculated the force field and vibrational spectra of formamide, acetamide, etc. and, as a larger step, also the dipeptide N-acetil-N'-metilalaninamide, all in an ab initio formalism, using a middle-size basis set (4–21). They are working on the excited and ionized forms (model compound N-metilacetamid) from both geometric and vibrational point of view, utilizing large basis sets.

In the theoretical part of the Department a small group led by Tamás Geszti (members are F. Pázmándi, I. Csabai and F. Czakó) are interested in neural network modelling. This research has two main goals: to get a better understanding of brain functions and to develop artificial networks, which can help to solve problems, hard for the traditional algorithms. They investigated the famous Hoppfield model and gave a new explanation for dream sleep. The Kohonen model of neural self-organization was also studied. They made some applications of these networks in data-processing, e.g. signal-peptid recognition in protein-, and quark-gluon separation in particle physics data.

Noémi Rozlosnik (leader of the Resonance Group of the Department) is using spectroscopic methods in biophysics, biochemistry and medical application. She investigates the biological membrane structure and free radicals in different biological systems by EPR and measuring EPR parameters of some iron and vanadium complexes. Computersimulation programs were developed for evaluation of complicated EPR spectra. She also measures heavy metals in air and biological samples by plasma-emission spectroscopy.

GÉZA MESZÉNA

BALATON LIMNOLOGICAL RESEARCH INSTITUTE OF THE HUNGARIAN ACADEMY OF SCIENCES, TIHANY

Sixty six years ago on the 5th of September, 1927 the opening of the first Biological Research Institute was celebrated in Tihany, Hungary. Accordingly, an old dream of many natural scientists has been realized: the natural biological research received an independent home with well-equipped laboratories of the time, with calm but stimulating atmosphere indispensable in scientific research.

From the point of view of the research work the Institute was given a double program: to study Lake Balaton on the one hand, and to study general biological and physiological problems on the other.

During the first two decades the Institute not only became famous among scientists in Hungary and abroad but provided research possibilities for several Hungarian and foreign scientists, too. There was almost nobody among the Hungarian biologists who, at that time, did not work once or several times in our laboratories.

Adhering to the principles of its foundation, scientific activities have been persued in different fields. Since 1962 a reorganization of the Institute took place. Two departments were organized: the Hydrobiological Department dealing with the problems of the Lake, and Zoologicaal (Neurobiological) Department focusing its attention on the nerve and muscle physiology of invertebrates. Since 1964 a substantial efforts were made in this Department to introduce the intracellular microelectrode technique in order to study the membrane properties of giant neurons in the CNS of molluscs. Later, on voltage-clamp and patch-clamp techniques were also introduced to study elementary processes of excitation. Although the Institute basically has no projects explicit biophysical profile a number of research and publications were from the topic of membrane biophysics of excitable membranes. The research was concentrated to study the passive and active electrical properties of cardiac and neuronal cell membranes, including voltage-dependent and voltage independent ionic channels, and the ultrastructure of the cells as well. Recently our studies are focused on heavy metal actions on excitable cells as well as on different transmitter and peptide effects. Immunocytochemical methods are used to determine the distribution and localization of neuropeptides and transmitter substances. The Zoological Department possesses biochemical and morphological laboratories giving multiple possibilities to study different themes. The Institute is equipped with HPLC (Waters), Atomic Absorption Spectrofotometer (Perkin Elmer 5100 PC), Liquid Scintillation Counter (LKB, 1211 Racheba) and scanning and electron microscopes. (Tesla). Recently the role of proton pumps are being studied during the fertilization of the roe of fish in order to elucidate the effect of acidification of the natural waters.

Thus, at both Departments there are excellent possibilities to perform experiments using different biophysical methods. The Institute owns a Guest House with 17 comfortable quest-rooms for visiting scientists.

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Balaton Limnological Research Institute of the Hungarian Academy of Sciences, Tihany

ISOTOPE DIAGNOSTICS AND RADIATION BIOLOGY IN BIOMEDICAL CYCLOTRON LABORATORY, DEBRECEN

The Biomedical Cyclotron Laboratory (BCL) was founded in 1987 with the aim to apply cyclotron facilities of the Nuclear Research Institute (NRI) of the Hungarian Academy of Arts and Sciences in medical care and biomedical research. The laboratory is headed by Professor Lajos Trón.

The staff of BCL consists of 8 teachers-researchers (5 physicists, 2 chemists, 1 medical doctor) and 3 technicians. They have the following positions: full professor (1), associate professor (1), principal investigator (1), senior investigator (1), junior investigator (3), resident (1). Two of them possess scientific degrees (1 person is doctor of biological science, 1 person is candidate of biological science), five have university doctor degree, one person is medical doctor. All staff members speak foreign languages.

In order to start neutron radiation therapy of patients within a reasonably short time a neutron source with Be as target material (using the external proton beam of the cyclotron) has been installed. The construction of the neutron producing target chamber was the result of a cooperation between coworkers of BCL and NRI. We characterized the radiation field of the Be + proton (18 MeV) neutron source by physical-dosimetric measurements; the energy spectrum of fast neutrons and the dose intensity distribution curves have been determined. Neutron irradiation experiments have been routinely carried out on cellular systems according to our own research projects and on various cellular and small laboratory animal systems in collaboration with members of other departments (University Medical School, Department of Radiology and Department of Microbiology; National Research Institute of Radiobiology and Radiation Hygiene; Kossuth Lajos University of Debrecen, Department of Ecology).

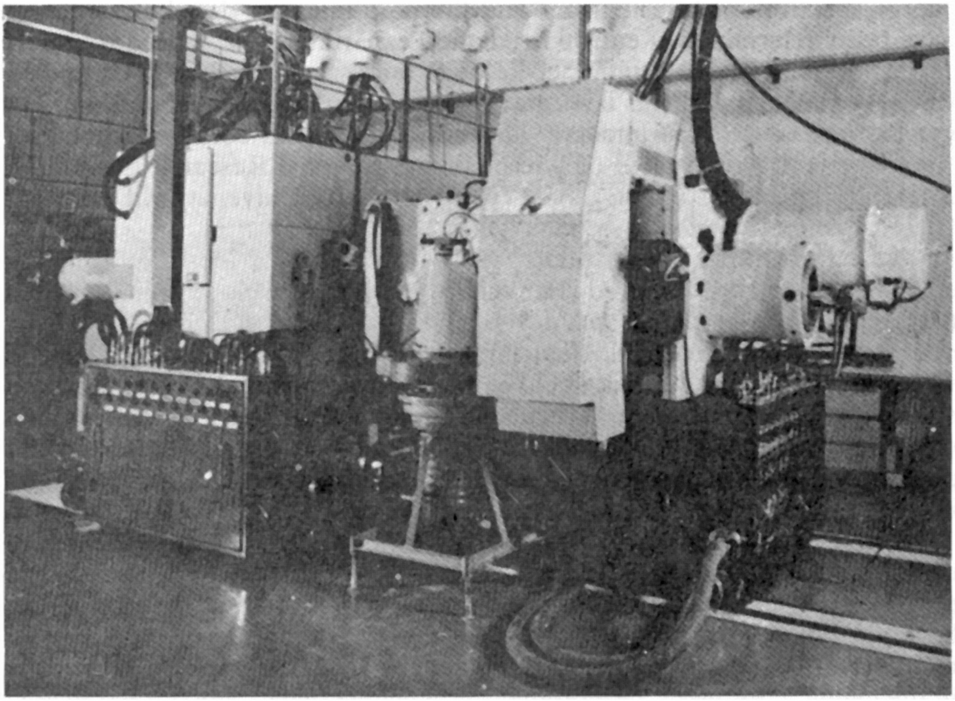
For neutron therapy of tumors of relatively deeper localization higher energy neutrons are required. For this purpose we developed and installed (partially as our research and development) a gas target chamber having deuterium as target material. Neutron and gamma dose intensity distributions were measured in the radiation field of this neutron source without collimation and also using a home made experimental collimator. The energy distribution of the fast neutrons produced was as well determined. Using results of water phantom measurements for deep dose distributions, dose intensity profiles and isodose curves have been constructed.

The cyclotron of NRI systematically produces short living radioactive isotopes used in nuclear diagnostic laboratories of the country. For labeling purposes ^{123}I and ^{67}Ga have been constantly produced since 1989 and the beginning of 1991, respectively. Nowadays sterile gallium (^{67}Ga) citrate is also manufactured as radiopharmacon. Our department being not involved directly in the manufacturing of these products is in charge of carrying out the related and necessary quality control investigations. These measurements include the control of nuclidic, chemical and radiochemical purity as well as sterility of the products. In the case of products (e.g. sterile gallium citrate injection) we also contributed to the development of protocols for quality control measurements and took part in the development and construction work allowing the preparation of sterile products.

To the efficient production of high chemical purity $^{111}In\ Cl_3$ aspiring to a large scale national consumption we developed and modified the protocol of the radiochemical separation. As a result we succeeded in producing $^{111}InCl_3$ of very good chemical purity with high radiochemical yield. Both parameters compare advantageously to the international standards. The product $^{111}InCl_3$ can be used as an intermediate to label antibodies and blood cells. The developed extraction apparatus serves as a good starting system for the future construction of an automatic version.

We are routinely carrying out diagnostic investigations with our planar scintillation camera. The number of investigations (scans) per year is around one thousand.

The planar scintillation gamma camera was obtained from Gamma Ltd, Budapest in 1987. At that time the first generation of data acquiring unit and the appropriate data processing software was not in the production line any more, while the second generation of these options was still in development. The lengthy development and the very high cost of these facilities made us



The MGC type Cyclotron of the Nuclear Research Institute of the Hungarian Academy of Sciences, Debrecen initiate a research and development program in cooperation with experts from other institutions. This program resulted in the installation of a system which is at least comparable to the second generation of the system by Gamma Ltd and it is currently used at many isotope diagnostic laboratories of the country.

In 1993 a Positron Emission Tomograph Center is being installed in Debrecen. The Biomedical Cyclotron Laboratory is in charge to operate the system and run and organize the research activity of the center. The installation was preceeded by an intensive radiochemical development program.

For ^{18}F production purposes we developed target chambers of different constructions. The optimized version requires a very small amount of ^{18}O enriched water as target material, – a critical point because of the high cost of the „heavy oxygenwater". The final version can be loaded with high ion currents required to match activity demands of PET investigations. We solved the synthesis of the inactive precursor of FDG (2-^{18}F-2-dezoxy-D-glucose) and the coupling of ^{18}F to the precursor. Based on NMR and HPLC quality control measurements the product is homogeneous, its radiochemical purity fulfills the requirements necessary for human in vivo diagnostic use. Procedure to register the product has recently been initiated.

Parallel to the development of the FDG synthesis a HEADS (high efficiency annihilation detecting system) program was developed aiming the coincidence detection of PET isotopes. The equipment, although not providing image formation, allows linear scans of the investigated systems. A stereometric mechanism has been constructed to the HEADS device and the panels for the required electronics have been worked out as well.

Before the installation of the PET camera transmembrane signalling was the main research field of the laboratory. Special attention was paid to the study of the spacial relationship of the membrane proteins. The laboratory contributed basically to the development of the flow cytometric energy transfer measuring technique. As a result of this the sensitivity of the method was increased and the investigation of systems with a lower level of antigen expression became possible. Expression of membrane antigens as well as the existence of macromolecular complexes on the cytoplasmic membrane was studied in cells of different phases of the cell cycle.

The regulation of intracellular ion concentrations in another field of interest. Special flow cytometric assays have been developed to measure intracellular concentration of monovalent cations. Alterations in these cellular parameters are studied during tumor progression.

Aiming a better understanding of cell demage by ionising radiation, cell parameters mentioned above (intracellular ion concentrations, supramolecular structure of membrane antigens, etc) are studied using samples exposed to radiation of different kind and different dose.

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