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MEDICAL RESEARCH CENTRE

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ON SCIENTIFIC ACTIVITIES
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MEDICAL RESEARCH CENTRE
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R E S E A R C H R E P O R T

STUDIES ON THE FUNCTION OF NERVOUS SYSTEM

Department of Neurophysiology
Head: Prof. Witold Karczewski

Functional organization of respiratory neural network -
- sources and mechanisms of the respiratory drive

ANALYSIS OF INTRAMEDULLARY AND MEDULLO-DIAPHRAGMATIC
CONNECTIONS

1/ Previous studies with the "split brain" preparation showed that in the rabbit and monkey there are two symmetrical relatively independent networks of respiratory neurones. In the cat the procedure stops the respiratory activity. However, this applies only to eupnoea; generation of the respiratory rhythm reappears with enhanced "respiratory drive" /hypercapnia, asphyxia/. Thus, the hypothesis that generation and transmission of activity to the respiratory motoneurones depends upon decussating connections within the medulla, had failed. Splitting the brainstem raises only the excitatory threshold of the respiratory neurones supposedly as the result of reducing the influx of non-specific excitatory stimuli. It has to be stressed that splitting the brainstem in the cat does not induce an "independent generation of the respiratory rhythms" observed in the rabbit and monkey. Species differences emphasize the risk of drawing general conclusions from the studies devoid of comparative values. In spontaneously breathing rabbits with split brainstem quantitative differences exist in the reaction of the phrenic and intercostal motoneurones.

2/ Chronically vagotomized rabbits showed undisturbed laryngeal function with the constrictory reaction to serotonin and no respiratory reaction to histamine injection. Chronic vagotomy produces pathological changes in the lung parenchyma:

dilation of the bronchi and bronchial emphysema and the inflammatory process associated with the longer survival times.

3/ In the clinical studies /carried out in cooperation with the Department of Anaesthesiology, Medical Academy, Warsaw/ of the patients undergoing surgery during controlled hypotension changes in the acid-base balance of CBF were shown. It is suggested that the drugs inducing hypotension might cause the opening of the arterio-venous anastomoses and thus should be applied with caution.

See the list of publications:

6, 8, 11, 12, 19, 25, 26, 27, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 65, 75, 76, 77, 102, 161, 174, 175, 176, 177, 178, 179, 187, 198, 204, 219, 220, 221, 222.

NEUROHORMONAL MECHANISM OF CARDIOVASCULAR REGULATION

Laboratory of Circulation Physiology

Head: Assoc. prof. Krystyna Herbaczyńska-Cedro

1/ Adrenaline and noradrenaline infusions induced a release of PGI_2 - like substance. After alfa-adrenergic blockade catecholamines were ineffective in releasing PGI_2 -like substance whereas beta blockade had no apparent inhibitory effect. The substance was unstable and its release was prevented by cyclooxygenase inhibitors. It seems likely that PGI_2 is released from contracting vascular tissue. The low release and delayed appearance of PGI_2 - in the circulation suggest that PGI_2 release may be evoked indirectly by other agents stimulated by catecholamines, such as angiotensin.

2/ The metabolic and haemodynamic effects of adrenaline were examined and no relationship between these effects was found. The different types of haemodynamic responses to the hormone cannot be attributed to the type of substrate utilized by the myocardium but to different rates of adrenaline clearance.

MECHANISM OF CARDIAC EFFECTS OF INOSINE

It was shown that inosine is a valuable therapeutic drug when applied in experimental cardiogenic shock. It increases cardiac output, cardiac muscle contraction, coronary blood flow and decreases end-diastolic pressure of the left ventricle.

PATHOMECHANISM OF CARDIAC HYPERTROPHY

Study on the role of beta adrenergic receptors in development of cardiac hypertrophy, induced by aortic constriction, revealed that the ratio of beta to alfa adrenergic receptors is increased during acute phase of this pathological condition. The absolute number of beta adrenergic receptor sites remains unchanged but the number of alfa receptors is significantly reduced. The total content of catecholamines in cardiac tissue was shown to decrease at the same time.

See the list of publications:

13, 15, 16, 17, 30, 61, 62, 97, 98, 206, 236, 237.

MECHANISMS CONTROLLING ENERGY METABOLISM AND HAEMODYNAMIC ADAPTATION UNDER PHYSIOLOGICAL CONDITIONS AND IN SOME CIRCULATORY AND METABOLIC DISORDERS

Department of Applied Physiology

Head: Prof. Stanisław Kozłowski

In order to evaluate the controversial problem concerning the role of the adrenergic system in the control of energy metabolism in acute energy deficit changes in the plasma catecholamine /CA/ concentrations were following during a few-day fasting dogs. It was found that the typical lipid mobilization, occurring in this situation, is accompanied by a progressive increase in both the plasma adrenaline /A/ and noradrenaline /NA/ levels. An attempt was made to elucidate importance

of the sympatho-adrenal system for the metabolic response to fasting, applying blockade of beta-adrenergic receptors with propranolol.

In further studies concerning the original concept of the glucostatic control of the adrenergic system activity hepatic glucoreceptors were proved to play an important role in the activation of this system under conditions of carbohydrate deficiency /prolonged physical exercise/.

Continuing the investigations on lipid metabolism during physical effort it was found that in dogs the increase in the muscle lipoprotein lipase activity /LPLA/ is proportional to the intensity of exercise. Besides, a relationship was demonstrated between the enzyme activity and the plasma free fatty acid concentration. In further study it was shown, that the muscle LPLA is largely affected by feeding state of animals. In dogs fed fat-rich meal the muscle LPLA at rest was markedly lower than in fasting state, and no exercise-induced increase in the enzyme activity occurred. In spite of it prolonged physical exercise performed by the dogs few hours following fat-rich meal was found to accelerate significantly the plasma chylomicron triglyceride /TG/ uptake by working muscles, which was accompanied by a diminished uptake of TG by adipose tissue in comparison with resting conditions.

Some other metabolic and neurohormonal responses to physical exercise were compared in fed and fasting dogs.

In the attempt of finding a measurable physiological index of psycho-emotional stress during occupational work changes in the urinary catecholamine /CA/ excretion were studied in 52 healthy human subjects performing a complex cognitive task. The increase in both the urinary adrenaline /A/ and noradrenaline /NA/ excretion was comparable to that found during physical work performed by the same subjects. Thus, measurements of the urinary CA excretion proved to be useful ⁱⁿ evaluation of mental and/or emotional overload.

The long-term studies were continued in 140 patients with coronary heart disease. These patients were examined twice a year during 7-12 years following myocardial infarction. Basing on clinical and physiological studies a diagnostic value of exercise-testing was evaluated. Moreover, recommen-

dations concerning the pattern of life, permissive everyday activities, and occupational work as well as therapy and rehabilitation were formulated.

Investigations were carried out on the effects of beta-blockers and digitalis on exercise tolerance and hemodynamics during physical effort in cardiac patients and healthy controls.

ENVIRONMENTAL INFLUENCES ON THERMOREGULATION AND RENAL MECHANISM OF THE EXTRACELLULAR FLUID VOLUME CONTROL

Investigations were carried out on the effects of acclimation to heat on thermoregulatory reactions to high environmental temperature and the hypothalamic thermal sensitivity in rabbits.

A decreased hypothalamic thermal threshold for vasomotor and respiratory reactions, and an increase in heat tolerance were found in the rabbits after prolonged exposure to high ambient temperature.

An increased heat tolerance was demonstrated in guinea pigs under nembutal anaesthesia.

Continuing the study on temperature regulation in surgical patients under general anaesthesia it was proved that changes in heat production and heat elimination, occurring both during surgery and the post-operative period, depend on type and site of surgery. Environmental conditions, mainly radiative and convective heat emission were found to influence significantly the thermal balance of these patients.

In further studies on a relationship between thermal and water balance it was demonstrated that dehydration attenuates panting response to intraventricular 5-hydroxytryptamine administration in the rabbit. Both this finding and previous results suggest that dehydration may modify signals generated in the brain thermoregulatory centres controlling evaporative but not vasomotor heat loss.

The last of a long series of investigations designed to evaluate the role of renal sympathetic nerves in the control of renal function was submitted for publication. The data show that in a chronically denervated kidney the tubules are

hypersensitive to circulating noradrenaline. They respond to the exogenous hormone with an increase in sodium re-absorption which is greater than that of the intact kidney. This is the first demonstration of tubular hypersensitivity - a phenomenon related to denervated artery hyperresponsiveness to catecholamines.

A method was developed for dynamic evaluation of the renal cortico-medullary electrolyte gradient on basis of tissue electrical conductance measured in an *in situ* kidney. Measurements were performed using stainless steel, gold-coated or iridium-platinum needle electrodes and best results were obtained with the last mentioned type of electrodes. In studies with anesthetized animals four electrode pairs /rabbit/ or six pairs /dog/ were inserted into the kidney and tissue conductance of different kidney zones was recorded during experimental maneuvers that are known to modify the renal electrolyte gradient. The method offers a unique possibility to follow the time course of electrolyte gradient changes in a living and functioning kidney. Electrolyte distribution in the renal interstitium forms a basis for processes of urine concentration and dilution.

See the list of publications:

9, 10, 45, 70, 71, 82, 84, 90, 91, 109, 110, 111, 112, 113, 114, 121, 142, 173, 180, 199, 200, 201, 202, 203, 218, 224, 226, 227, 231, 238.

EFFECTS OF HYPOXIA ON BRAIN MEMBRANE METABOLISM AND BIOCHEMICAL PROPERTIES OF SYNAPTIC ENDINGS

Department of Neurochemistry

Head: Assoc. prof. Jerzy Łazarewicz

The study was continued on the composition and metabolism of brain membrane lipids and proteins concerning the alternations of these compounds during hypoxia and ischemia. It was found that 10 min brain ischemia in Mongolian gerbil /*Meriones unguiculatus*/ produces reversible changes in physicochemical

properties of soluble and microsomal proteins in brain manifested by an increase of protein sedimentation in crude mitochondria /P₂/ fraction. It was noted that during mild hypoxia /7% O₂ in N₂/ activation of protein degradation occurs in several subcellular fractions of the rat brain.

A stimulatory effect of calcium ions on "in vitro" protein degradation by neutral proteinases was found, suggesting that calcium may also activate protein degradation in vivo.

It was shown that ischemia in gerbil brain during the first 30-60 s. significantly increases the pool size of brain arachidonic acid. It was demonstrated that enzymatic degradation of phosphatidylcholine and phosphatidylinositol by phospholipase A, phospholipase C and also neutral glyceride lipases are responsible for liberation of arachidonic acid.

The mechanism of monoacylglyceride lipase regulation in brain was defined. An increase of this enzyme activity after hypoxia /5% O₂ in N₂/ and the first 30 s. of ischemia was observed.

It was shown that acute hypoxia /1% O₂ in N₂/ resulted in a selective decrease of arachidonic acid incorporation into phosphatidylinositols /PI/ whereas the treatment of synaptosomes with bovine serum albumin and dithiothreitol caused an suggest that, in vivo, during brain hypoxia as well as during preparation of synaptosomes the endogenous inhibitor of the arachidonate transfer into phosphatidylinositol is liberated. Some metabolic and functional properties of brain synaptosomes were characterized and the effect of hypoxia on these properties was studied.

The membrane potential of metabolically intact /well preserved/ synaptosomes was determined and the effect of K⁺, Ca⁺⁺ and Sr⁺⁺ ions, pH and some inhibitors on the membrane potential was investigated.

It was shown that high affinity uptake of ³H-GABA into brain synaptosomes may be attributed to not accumulation of this neurotransmitter but not to hemoexchange.

The incubation of synaptosomes for 20 min at 25°C in anaerobic conditions at pH 6,0 /in vitro model of hypoxia and ischemia/ leads to the efflux of K⁺ ions from synapto-

somes into the incubations medium. It was demonstrated that this effect is completely reversible after restoration of aerobic conditions. These findings suggest that permanent loss of brain function following prolonged hypoxia and ischemia does not seem to be related to the irreversible damage to the synapses with respect to their K^+ leakage but rather to the impairment of some other neuronal functions.

It was demonstrated that hypoxia /5% O_2 in N_2 / has no effect on the accumulation of noradrenaline and Na^+-K^+ -ATPase activity in the brain synaptosomes. However, brain hypoxia modifies the glycoprotein composition of synaptosomal membranes and abolishes the stimulatory effect of adrenaline on Na^+-K^+ -ATPase activity in synaptosomes.

The studies on the role of astroglia in the inactivation of peptide putative neurotransmitter enkephalin in the brain indicated that enkephalines are not accumulated by glioma and neuroblastoma cells in culture. These cells were found to degrade Leu-enkephalin by amino and carboxypeptidases located on the outer surface of the cell membrane.

See the list of publications:

7, 24, 28, 29, 78, 115, 116, 117, 140, 141, 167, 168, 183, 208, 209, 210, 211, 212, 213, 214, 215, 235.

STUDIES ON THE STRUCTURE AND BIOLOGICAL PROPERTIES
OF THE NERVOUS TISSUE

Department of Neuropathology
Head: Prof. Mirosław J. Mossakowski

Nerve tissue reaction to endogenous and exogenous
damaging factors

STRUCTURAL AND METABOLIC DISTURBANCES IN THE CENTRAL
NERVOUS SYSTEM UNDERLYING COMATOUS STATES IN HUMANS
AND IN EXPERIMENTAL ANIMAL MODELS

In investigations on the pathomechanism of central nervous system impairment in hepatic diseases, a "chemical" model of hepatic encephalopathy has been worked out in which liver is damaged by thioacetamide - a strong hepatotoxic agent. Two intraperitoneal injections of the compound into rat /250 mg/kg body weight/ at 24 h intervals evoke biochemical changes in the brain typical for hepatogenic encephalopathy: a rise in the enzymatic activities related to glutamine synthesis and changes in the γ -aminobutyric acid /GABA/ level similar to those observed following the application of the portocaval shunt. The biochemical changes precede the appearance of morphological features of encephalopathy, mainly consisting in the proliferation and hypertrophy of astrocytes. In the serum of animals subjected to thioacetamide treatment increased levels of ammonia and phenolic compounds were found. Administration of thioacetamide to the organotypic culture of astrocytes produced in these cells changes identical to those observed in hepatogenic encephalopathy, including the formation of Opalski's cells. The above changes can be easily distinguished from non-specific cytotoxic effects following direct administration of thioacetamide to the culture.

In the investigations on the pathomechanism of central nervous system damage in renal failure the deposition of immunological complexes in the central nervous system of the rabbit was examined. Such complexes are formed in the conditions of chronic serum sickness, which was produced experi-

mentally by administration of bovine serum albumin. The process of deposition was accompanied by disturbances in the blood-brain barrier and cerebrospinal fluid-brain barrier, inflammatory changes in cerebral blood vessels and the appearance of perivascular necrotic foci. In rats with uraemia, evoked by nephrectomy, morphological changes in the central nervous system appear to be identical to those previously observed in uraemic humans, except for the absence of immunopathological symptoms.

In studies on the binding of carbon tetrachloride to nucleic acids of the liver, data have been obtained indicating that phosgene - one of the major metabolites of CCl_4 - may be the interacting intermediate. This compound was shown to react with the phosphate groups on pyrimidine nucleotides and with the purine ring in the conditions of chemical synthesis.

A new, simple procedure has been developed for the isolation of astrocytes from the rat brain. The cells were characterized with respect to their macromolecular composition, the ability to incorporate a precursor ^3H uridine/ into RNA, and the activity of two enzymes: astrocyte - specific glutamine synthetase and glutamic acid decarboxylase as a marker of contamination by neuronal elements. The tests confirmed satisfactory purity and well-preserved biological activity of the cell preparation.

It was demonstrated that the astrocytes are rich in specific insulin receptors, which may indicate a role of these cells in the uptake and distribution of the hormone in the central nervous system.

PATHOGENETIC MECHANISM OF THE VASOGENIC DAMAGE OF THE CENTRAL NERVOUS SYSTEM

The recovery of spontaneous bioelectric activity of the brain and the changes in blood pressure as well as in the respiratory and cardiac function were evaluated in Mongolian gerbils subjected to 30 min cerebral ischemia. The recovery of brain activity with a tendency towards normalization after prolonged ischemia is followed by progressive structural

changes with predomination of cytotoxic edema leading to brain death. Experiments on rabbits revealed that disconnection of cerebral circulation is accompanied by neurogenic stress characterized a.o. by the release of ACTH and large amounts of cortisol into blood.

The recovery of spontaneous bioelectric activity in the rabbit brain, following complete ischemia was found to occur after ischemia periods as long as 60 min, whereby the activity of the respiratory centres recovered faster than that of the cerebral cortex. Complete cerebral ischemia is accompanied by a number of more general changes in the organism, such as release of adrenaline and noradrenaline into blood, disturbances of heart function, a marked increase of blood pressure changing in the later periods into severe arterial hypotension etc. Despite the recovery of the cerebral activity, prolonged ischemic periods lead to the development of irreversible structural changes.

Morphological and histochemical studies of the pial vascular net in the rabbit concentrated on evaluating density of the adrenergic and cholinergic nerve fibres in the active portions of the vessels in relation to the neurogenic mechanism of autoregulation.

Indomethacin - an inhibitor of prostaglandines - was demonstrated to alleviate the development of cerebral microcirculation disturbances following ischemia.

Structural and ultrastructural changes in neurohypophysis of patients who died following cerebral stroke were described, with a focus on regressive changes in neurosecretory axons and degenerative forms of pituicytes.

THE BIOLOGICAL PROPERTIES OF THE NERVOUS TISSUE AND THE EFFECTS OF ENDO- AND EXOGENEOUS CHEMICAL FACTORS AS A BASIS OF DEGENERATIVE PROCESSES

Morphology of the rat neurons in the organotypic culture of striatum at different stages of maturation and differentiation was studied with the aim to establish a reference for the evaluation of pathological changes. Electron microscopic examination allowed to distinguish 5 ultrastructurally

different types of nerve cells, but not earlier than on the 10th day of the growth. The most numerous were the type I neurons corresponding to medium size striatal neurons occurring *in vivo*.

Administration of kainic acid - a neurotoxic analogue of glutamic acid - either to the rat striatum *in vivo* or to striatal cultures *in vitro* - produces primarily characteristic changes in astrocytes. Fibrous gliosis observed *in vivo* appears to genuinely reflect similar changes occurring in striatum of patients with Huntington chorea while *in vitro*, an excess accumulation of gliofilaments and gliotubules in astrocytes accompanied by neuronal changes indicates a direct effect of the agent on astroglia.

Studies on maturation of the mouse substantia nigra in organotypic culture revealed the outgrowth of dopaminergic fibers from the explantate to precede the migration of glial cells. The presence of anatomically and functionally related striatal cells in the culture appears to prevent early degeneration of substantia nigra neurons and processes, which emphasizes the significance of the dopaminergic system integrity.

Investigations on the manganese encephalopathy included examination of the effect of manganese on the rat cerebellar cultures *in vitro*. The predominant changes observed were the damage of glial mitochondria and rough endoplasmic reticulum, finding biochemical manifestation in the decreased activity of respective dehydrogenases. The effect of manganese introduced parenterally on the rat brain tissue, as evaluated by light microscopy, consists in vacuolization of white structures, accompanied by a weak astroglial reaction and neuronal degeneration in Ammon's horn, substantia nigra and thalamus. Electron microscopic examination revealed severe damage of neurons and glia in the form of swelling and enlargement of mitochondria with a complete loss of cristae and formation of giant vacuoles. The mitochondrial changes were more pronounced in the axons than in perikarya and were indicative of cytotoxic edema.

Investigations on the effects of oncogenic agents on the central nervous system were performed using two methylating

compounds: methylnitrosourea /MNU/ and ethylnitrosourea /ENU/. Immunofluorescence studies in the rat cerebellar cultures demonstrated an increased fluorescence of glial cells /astrocytes/ in particular following the administration of MNU. This finding suggests an increased synthesis of the glial specific antigens under the influence of carcinogen. ENU given intravenously into mice causes a transient damage of capillary endothelium, most probably by facilitating the permeation of myelin debris and other nerve tissue elements into the vascular bed, which may play an essential role in further development of immunologically-based demyelination processes.

Investigations on the role of neurotransmitters and their metabolites in the pathogenesis of a number of central nervous system diseases in humans have been initiated. The γ -aminobutyric acid /GABA/ and homovanilic acid /HVA/ levels were determined in the cerebrospinal fluid of epileptic patients. Although the tests revealed a decrease of GABA levels in patients it has not been definitely established whether this is due to the long term treatment of the patients or to development of the pathological process itself.

See the list of publications:

1, 2, 3, 4, 63, 64, 72, 73, 74, 79, 80, 85, 86, 88, 89, 128, 129, 130, 131, 133, 134, 135, 136, 137, 138, 139, 184, 205, 233.

THE DEVELOPMENT OF THE NERVOUS SYSTEM UNDER NORMAL AND DISTURBING ITS STRUCTURAL MATURATION CONDITIONS

Laboratory of Developmental Neuropathology
Head: Prof. Maria Dąbka

Chronic intoxication with organophosphorus inhibitors of acetylcholinesterase leads to psychiatric deviations in men and behavioral disorders in animals. The effect of dichlorvos, one of such inhibitors, on the level and metabolism of monoamine neurotransmitters in brain was studied during postnatal development. Chronic treatment of young rabbits

with dichlorvos decreased serotonin level in some brain regions /mesencephalon, brain stem, hippocampus/. The level of total serotonin in blood of these animals was also significantly lower than in untreated animals. The permeability of blood-brain barrier was unchanged following dichlorvos treatment, so serotonin did not penetrate through this barrier. The activity of monoamine oxidase mainly the B form of the enzyme, decreased after dichlorvos. The turnover rate of serotonin in two functionally different groups of the brain structures was also studied. Dichlorvos increased availability of serotonin in the brain regions connected with behavioral reactions in animals /neocortex, hippocampus/ and decreased turnover rate of the amine in the regions related to motor function /brain stem, spinal cord/.

In the separate series of experiments the effect of cyclophosphamid /cytostatic drug/ was examined in the rabbits during their development. Young animals tolerated well the prolonged /6 days/ treatment with the drug /16 mg/kg/day/. However, some changes in blood /total leucocytosis decreased to 37% and amount of granulocytose to 26%, lymphocytose to 60%/ were found. With the higher doses of the drug the changes were more pronounced and in younger animals the reaction was more pronounced than in older ones.

See the list of publication:

14, 20, 21, 22, 23, 99, 100, 122, 123, 124, 125, 126, 127, 232.

THE EFFECT OF CEREBRAL ISCHEMIA ON THE ULTRASTRUCTURE OF
THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM OF THE MONGOLIAN
GERBIL

Laboratory of the Ultrastructure of the Nervous System
Head: Prof. Jerzy Borowicz

The hypothalamo-neurohypophyseal system of Mongolian gerbils subjected to experimental cerebral ischemia was examined by means of the EM technique. The studies concerned secretory neurons and synaptic boutons in the supraoptic /SO/ and paraventricular /PV/ nuclei as well as the neurosecretory axons and pituicytes in the neurohypophysis.

/I/ Hypothalamus. The SO and PV secretory neurons of gerbils with brain ischemia exhibit features characteristic for an increased cell activity in the form a developed Golgi complex, widened RER cisternae and numerous polyribosomes. This refers particularly to PV neurons in which numerous lysosomes are also present. The synaptic boutons show distinct ultrastructural changes. These changes are manifested in an increased polymorphism of the synaptic vesicles, the occurrence of "ballooning" vesicles, vesicle aggregation, a reduced number of vesicles or electron-transparent axoplasm.

/II/ Neurohypophysis. In gerbils with brain ischemia most secretory axons in the neurohypophysis are well preserved and as regards ultrastructural organisation they do not differ from the control. Some axons show ultrastructural changes and are characterised by the absence of neurosecretory granules, smooth endoplasmic reticulum proliferation or myelination with simultaneous obliteration of the primary structure. The Golgi complex is greatly enlarged in the pituicytes.

Gerbils with brain ischemia exhibit a low ATP-ase activity. It is practically noticeable only in the synaptic boutons with ballooning synaptic vesicles.

The above described observations indicate that in a state of brain ischemia changes occur in the ultrastructural picture of the secretory neurons of the SO and PV nuclei of the hypothalamus and of the secretory axons and pituicytes in the neurohypophysis. At the same time structural changes within

the synaptic boutons are an evidence of a previous active state of the synapses or of their impairment.

Beside investigations on brain ischemia, studies were continued on the influence of normobaric hyperoxia on an immature organism. It was demonstrated that, under normobaric conditions, oxygen excess changes the permeability of the cell membranes in the brain cortex and lungs of the rabbit impairing their metabolism and ultrastructure. The degree of injury to the immature brain cortex and lungs depends on the duration of hyperoxia, whereas the dynamic of the changes is related to the rabbit's age. With longer lasting normobaric hyperoxia a chronic lung oedema and cytotoxic brain oedema develop. A further consequence is lung fibrosis and irreversible changes in the glial and nerve cells of the immature brain cortex. Investigations have been started concerning the influence of normobaric hyperoxia on the adrenals, kidneys, liver and myocardium of young rabbits.

Beside the basic problems of the Laboratory the studies have been initiated in collaboration with some other Medical Institutions. The studies concerned some problems of developmental neuropathology, ultrastructural changes in nervous system during chronic Li_2CO_3 intoxication, and some biochemical and ultrastructural features of peripheral human lymphocytes of patients suffering from chronic lymphatic leukemia.

See the list of publications:

31, 32, 33, 34, 35, 36, 39, 40, 41, 42, 43, 44, 69, 87, 103, 104, 105, 106, 107, 108, 132, 188, 230.

CLINICAL METHODS FOR THE EARLY DETECTION OF MALFUNCTIONS
IN THE INTRACRANIAL PRESSURE - VOLUME RELATIONSHIPS IN
PATIENTS WITH INTRACRANIAL PATHOLOGY

Department of Neurosurgery
Head: Assoc. Prof. Eugeniusz Mempel

Further studies concerning the development of the computerised intensive care system were carried out.

In experimental studies a new animal model was introduced applying inhalation anaesthesia. Pilot investigations were performed on the effect of increased intracranial pressure on respiration and the cardiovascular changes, mainly the ECG pattern.

See the list of publications:
18, 58, 59, 60, 83, 223.

DISORDERS OF SPEECH AND OTHER GNOSTIC FUNCTIONS IN CENTRAL
NERVOUS SYSTEM LESION

Department of Neurosurgery
Assoc. Prof. Jadwiga Szumska

A programme of studies on speech disorders in children has been started, with the aim of developing clinically useful methods of examination and rehabilitation of children with aphasia and other kinds of speech disorders. This project is a continuation of previous studies on speech disorders in adults, being however adapted to suit the special characteristics of these disorders in adolescence. The studies are conducted in a comprehensive way and include investigations of adolescent aphasia, intelligence quotient, visual and auditory perception.

EFFECT OF "PT" MUTATION ON NEURONAL CIRCUITS

Department of Comparative Neurology

Head: Assoc. Prof. Irmina Zelman

Investigations on hereditary degenerative neurological disease in pt rabbits were continued.

Light microscopic study of the brainstem reticular formation revealed permanent involvement of this structure in the pathological process as well as in acute and in chronic phase of the disease. Typical neuronal changes in the form of cytoplasmic swelling, patchy tigrolysis and nerve cell disintegration accompanied by glia proliferation predominated in the acute phase of the disease, whereas nerve cell loss, sclerotic neurons and rarefaction of nerve fibres characterized protracted and chronic course of this disorder. The pathomorphological abnormalities, generally of moderate degree, varied in intensity, RF-structures being the most intensive in the upper medulla and pontine tegmentum. Disseminated abnormalities of nerve cells and nerve cell processes may create the background for the disturbances of RF integrative function.

Preliminary biochemical investigations on isolated myelin proteins of the symptomatic pt rabbits /6- and 9-week old/ and control animals of the same age revealed an elevation of intermediate protein fraction and a decrease in proteolipid protein fraction in pt rabbits, suggesting retardation of myelin sheath development.

Electron microscopic study performed in the pt rabbits in the early clinical symptoms showed abnormalities which may indicate their metabolic insufficiency. These oligodendroglia changes may play a role as one of the factors responsible for the disturbances of myelin development.

STUDIES ON TRANSPLANTATION AND EXPERIMENTAL SURGERY

Department of Surgical Research and Transplantation
Head: Prof. Waldemar Olszewski

SPECIFIC MIGRATION OF LYMPHOCYTES AND MACROPHAGES
TO THE SITE OF ANTIGEN DEPOSITION

The studies on specific recruitment of lymphocytes were carried out on two models. In one, the kinetics of accumulation of cells were studied in lymphoid and extralymphoid tissues of normal rats given i.v. lymphoid cells obtained from enhanced /E/ and unmodified /U/ heart allograft recipients. Major differences in migration of lymphocytes from E and U rats were observed. Labelled cells from E rats transferred day-9 accumulated promptly into the lymph nodes and peripheral blood of test animals /75% of total dose recovered/, declining reciprocally in liver and spleen /25%/. Then, total activity in lymphoid and non-lymphoid tissue stayed relatively constant until 4 days grafting: levels coincident with those occurring during acute rejection at 6-8 days in U rats. Thereafter, accumulated activity in lymphoid tissues after transfer of lymphocytes from E rats decreased to 65% / $p < 0.01$ / before declining eventually to physiological levels /50-55%/ during ultimate graft rejection at approx. 25 days. The initial decline after 4 days coincided with a transient and self limited rejection episode typically occurring during the same time.

In another model, the non-specific migration of peritoneal exudate cells /PEC/ given i.v. to mice with intraperitoneally implanted tumors was studied. Mouse Ehrlich carcinoma cells and human K 562, MOLT4 and CCRF neoplastic cell lines were used. Syngeneic and xenogeneic non-neoplastic cells served as controls. The results obtained indicate that the "inflammatory" reaction evoked in the peritoneal cavity by tumor cells facilitate accumulation of the non-immune PEC in quantities measurable with the isotopic techniques. Accumulation of radioactivity in the peritoneal cavity with implanted Ehrlich ca cells was 0.524%, K 562 0.175%, CCRF 0.232% of the i.v. injected dose, with controls at the level of 0.015%.

INFLUENCE OF HYPERTHERMIA ON DISTRIBUTION OF THE RECIRCULATING POOL OF LYMPHOCYTES

The kinetics of distribution of recirculating lymphocytes in the state of hyperthermia /39°C, 8h/ was studied in rats using ⁵¹Cr-labelled mesenteric lymph node cells. Labelled cells were given i.v. at the beginning of the warming period. A significant redistribution of cells as compared with the controls was found. During hyperthermia lymphocytes migrated predominantly to the bone marrow /23% of injected dose, control 11-17%. There was a decrease in accumulation of cells in the spleen /14%, control 18%/ and lymph nodes /0.85-0.9%, control 1.7-2.05%. When different bone marrow compartments were evaluated, most of the specific activity /g was found in the bones of hind limbs. The results obtained indicate that the neurohormonal response to hyperthermia affects lymphocyte distribution, presumably due to an increased release of cortical hormones. The pattern of observed changes has been found similar to that demonstrated after systemic administration of corticoids.

RATE OF CAPILLARY TRANSPORT OF IMMUNE PROTEINS TO THE INTERCELLULAR SPACE

One of the basic questions in immunology is whether the concentration of the amount of humoral factors in the interstitial space is of primary importance in the immunoregulatory processes. In order to get some more insight into this problem studies were carried out on human volunteers. Changes in the concentration of various immune proteins in lymph, the representative of mobile tissue fluid, were evaluated under the condition of changing capillary filtration rate. Generally, concentrations of immunoglobulins in lymph were inversely proportional to their molecular weight, with the mean daily level of IgM in the range of 6-10% of that in serum. Elimination of the gravity factor from the hydrostatic pressure over a 24th period brought about an increase in the concentration of IgM to the highest of 25%. A rise in the hydrostatic component of the filtration process decreased the concentration of immuno-

globulins but increased their influx /volume/. No increase in capillary permeability was observed under these conditions. The results obtained so far indicate that under normal conditions the concentration of tissue fluid immunoglobulins can not reach the serum levels. An increase in the hydrostatic pressure in the capillaries promotes immunoglobulin transport together with the water flux, which results in a decreased concentration of protein. This is due to the rise in the filtration surface area and not to the permeability coefficient.

DEPENDENCE OF THE HEART ALLOGRAFT SURVIVAL TIME ON TYPE OF DONOR ANTIGEN USED FOR PRETREATMENT OF THE RECIPIENT

Administration of donor immune cells and allo-antiserum against donor histocompatibility antigens to the recipient results in a significant prolongation of heart allograft survival time. In 1981 further studies on the types of cells and their surface antigens responsible for this effect were carried out. It was found that the lymph node cells of donor type given to the heart recipient, across the major histocompatibility complex barrier, on day 11 are most powerful in prolonging the graft survival. Immunological characteristics of the subtype/s/ of these cells are studied.

RESPONSE OF SUPPRESSOR CELLS IN PERIPHERAL BLOOD OF SURGICAL PATIENTS

The operative trauma brings about changes in the reactivity of circulating mononuclear cells. These changes become superimposed on the immune processes developing in the course of cancer growth and transplant take. In the studies on characterization of suppressor cells in peripheral blood of patients undergoing surgery a substantial decrease in the percentage and activity of these cells was found on day 1-3 after surgery. This phenomenon may be accounted for by involvement of the suppressor cells in the wound healing, depriving the peripheral blood temporarity of this subset. The effect

of attenuated suppressor activity in blood on cancer growth and transplant take will be further studied.

See the list of publications:

5, 37, 38, 57, 66, 67, 92, 93, 94, 95, 96, 101, 118, 119, 120, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 162, 171, 172, 189, 190, 191, 192, 193, 194, 195, 196, 197, 207, 228, 229.

Laboratory of Experimental Surgery
Head: Assoc. Prof. Maciej Borkowski

Clinical observations indicate that in case of peripheral blood circulation disorders electrical transcutaneous stimulation has a pain allevating effect resulting also in general improvement in the state of the patients limb.

To study the mechanism responsible for the beneficial, clinical effects of electrical transcutaneous stimulation, experiments were carried out on cats applying the following methods:

- I - biological, based on the evaluation of blood platelet disaggregation on a collagen organ continuously washed with the animals blood.
- II - ADP platelet aggregation test consisting in continuous light transmission measurement through platelet rich plasma.

Electrical stimulation of the sympathetic chain transected at the L_2-L_3 , L_3-L_4 level confirmed in cats a relationship between direct stimulation of the sympathetic nerves and release of platelet disaggregating substance into the circulation.

Transcutaneous stimulation of the hind limb caused progressive disaggregation of blood platelets, indicating release of a substance with similar properties. The substance did not lose its properties on passing through lung circulation. The disaggregation was inhibited by indomethacin /10 mg/kg/. The test carried out with a delay period between

the release and application of the disaggregating substance /in order to allow for its decomposition/ showed that the metabolites retain properties of the original substance but they are less active.

The obtained results indicate that a prostacyclin-like substance is released into the circulation during electrical transcutaneous stimulation. This effect may predestinate transcutaneous stimulation for application as one of the supporting methods in treatment of certain peripheral circulation disorders.

OTHER RESEARCH WORKS

THE DYNAMIC PATTERN OF APTITUDE AND INTEREST DEVELOPMENT OF YOUNG INDIVIDUALS IN THE ASPECT OF MENTAL HEALTH

Research Group of School-Psychohygiene
Head: Dr Henryk Osieński, M.D.

The purpose of the reported investigations was a descriptive study of college students in a city environment in respect to the following basic factors: intelligence, special aptitudes, interests and personality traits. The investigations were both longitudinal and horizontal, and they were conducted by comparative methods. The comparisons were made between students of classical, natural science and mathematical profile classes.

The methods used in this study are generally known and recognized by psychologists. They include:

- Wechsler scale for measuring general intelligence level.
- Employee Aptitude Survey of Grimsley, Ruch, Warren and Ford for measuring special aptitudes such as verbal, perceptual, intellectual and motor aptitudes.
- Kuder's Preference Record Vocational - for measuring the interests in ten broad fields of life activity.
- Maudsley Personality Inventory of Eysenck.
- Latent Anxiety Test of Cattell.
- Gough's California Psychological Inventory.

Moreover, to investigate the interest in the subjects taught in schools an original method of its measurement, evolved by this team, was applied.

Most of the scholastic achievements of the students were analysed basing on marks received by them. The un-measurable scholastic achievements were checked asking the students questions according to a specially constructed inquiry form. The answers were verified by the teachers for ensuring full objectivism of the obtained results.

The results of this study are of theoretical as well as practical importance. In the theoretical aspect the problem of the students development and direction of the aptitudes and interests will be analysed in the life period when their importance in the individual's life is of decisive character for his further fates.

In the first stage of the study 330 students in classes of classical education, natural sciences and mathematical profiles were tested. Each student was tested by all methods mentioned above. In each case 78 measurements of various psychic traits were obtained. The very time-consuming and work-consuming analysis of the individual results have already been completed. In accordance with the time-table of this five-year study a multidirectional statistical analysis of these results is planned.

See the list of publications:
163, 164, 165, 166.

Mental Health Department
Head: Dr Zbigniew Poseł, M.D.

SOCIAL PARASITISM AND ITS CAUSES

Social parasitism is one the social pathology phenomena. The interdisciplinary investigations on this problem were carried out in Łódź - the large agglomeration of town population. The aims of these investigations are as follow:

- diagnosis of the physical and mental health conditions as well as the type of environment of the so-called social parasites,
- finding out the reasons for avoiding work,
- establishing the direction of preventive activity.

Two groups of men have been used in this study: 1/ men working in big factories, 2/ individuals avoiding work. All subjects of the two groups were examined directly and individually by specialists in internal medicine, psychiatrists, clinical psychologists and sociologists. Juridical investigation of the court documents relative to all persons of the two groups has been applied by an jurist.

FORMS OF DISFUNCTIONAL BEHAVIOURS IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS WITH VARIOUS TYPES OF MENTAL DISORDERS

It has been shown in epidemiological research that approx. 15% of children and youngsters demonstrate various mental disorders. This percentage increases in the adolescence period. Mental disorders are generally recognized as basic factors causing development of various forms of disfunctional behaviours. The object of the examinations has been a group of 300 subjects aged 15-18 with mental disorders /neurosis, behaviour disorders and mental retardation/.

The goal of research is to separate two groups /demonstrating and failing to demonstrate disfunctional behaviours/ from the individuals with mental disorders.

Comparison of the psychosocial factors differentiating these groups let to show the environment elements remarkably preventing formation of disfunctional behaviours.

LIFE STABILIZATION IN ALCOHOL-DEPENDENT ADULTS

Investigations have been initiated on the problem of life stabilization in adult human subjects dependent on alcohol. The present research deals with 100 alcohol-addicts /males/ aged approx. 40 years who examined for the first time

in 1970-71. The aim of the present study was a detailed medical and sociological analysis of personality, behaviour and life conditions of the same subjects during the last 10 years.

PSYCHO-PHYSIOLOGICAL AND SOCIAL DETERMINANTS
OF THE ACTIVITY IN PATIENTS AFTER
MYOCARDIAL INFARCTION

Myocardial infarction alters the social activity of an individual. The recovery should be then considered not only in medical but in psychosocial categories. Thus, the complex psychophysiological and psychosocial studies should stimulate the planning of most fruitful forms of rehabilitation. It might be expected that using these forms various destructive components and negative factors during treatment and rehabilitation could be diminished or even eliminated.

See the list of publications:

68, 81, 169, 170, 181, 182, 185, 186, 216, 217, 225, 234.

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VISITS ABROAD

Department of Neurophysiology

- Budzińska K. Nobel Institute, Stockholm, Sweden
- Grieb P. Department of Physiology University of Pennsylvania, Philadelphia, USA /long term visit/
- Huazczuk A. Harbor General Hospital UCLA, School of Medicine, Los Angeles, California, USA /long term visit/
- Pokorski M. Institute of Environmental Medicine University of Pennsylvania, Philadelphia, USA /long term visit/
- Romanjuk J. Nobel Institute, Stockholm, Sweden

Laboratory of Circulation Physiology

- Herbaczyńska-Cedro K. Midhurst Medical Research Institute Midhurst, Great Britain /long term visit/

Department of Applied Physiology

- Brzezińska Z. Swedish Institute Department of Hufvinge, Sweden /long term visit/
- Budohoski L. Department of Biochemistry University of Oxford, Great Britain
- Chwalbińska-Moneta J. Department of Clinical Physiology, Central Hospital of Etelä-Pohjanmaa, Finland
- Grucza R. Faculte de Medicine Laboratoire de Physiologie Lille, France /long term visit/

- Kaciuba Uściłko H. Department of Physiology, University of Genova, Genova, Switzerland
Institute of Experimental Endocrinology, Bratislava, Czechoslovakia
- Kapitaniak B. Faculte de Medicine University P.M. Curie, Paris, France
- Kozłowski S. Central Hospital of University Helsinki, Finland
Department of Biology of Physical Activity Jyväskylä University, Finland
Department of Clinical Physiology Seinäjoki Central Hospital, Finland
Department of Physiology Institute of Occupational Health, Helsinki, Finland
Institute of Experimental Endocrinology, Bratislava, Czechoslovakia
Research Institute of System Blood, Kolonia, GFR
- Nazar K. Central Hospital of University Helsinki, Finland
Department of Biology of Physical Activity Jyväskylä University, Finland
Department of Physiology Institute of Occupational Health Helsinki, Finland
Institute of Experimental Endocrinology, Bratislava, Czechoslovakia
- Niewiadomski W. Max-Plank Institut für System Physiologie, Dortmund, FRG
- Sadowski J. Arbeitsgruppe für Experimentelle Anästhesie Freie Universität, Berlin
- Ziemba A. Department of Physiology Institute of Occupational Health Helsinki, Finland

D e p a r t m e n t o f N e u r o p a t h o l o g y

- Albrecht J. Institute of Occupational Health, Helsinki, Finland
Institute of Molecular Biology, State University of Utrecht, Netherland
/long term visit/

- Gadamski R. Institute of Physiology Georgian Academy of Sciences Tbilisi, USSR
National Institute of Health, Bethesda, USA /long term visit/
- Kida E. Institute of Neurology Academy of Medical Sciences USSR, Moscow, USSR
- Mossakowski M.J. Institute of Physiology Georgian Academy of Sciences, Tbilisi, USSR
Institute of Reanimation Academy of Medical Sciences USSR, Moscow, USSR
Institute of Pathology; Institute of Anatomy Copenhagen, Denmark
Neurologische Klinik Kantonsspital Aarau
Clinic of Neurology Aarau
Clinic of Neurology Lausanne, Switzerland
- Rap Z. Institute of Physiology University Tübingen, FRG
Zentrum für Neurochirurgie am Klinikum der Justus Liebig-Universität Giessen, FRG
/long term visit/
- Renkawek K. Pavlov Institute of Physiology, Leningrad, USSR
- Szumańska G. University of Helsinki, Department of Anatomy, Helsinki, Finland
- Weinrauder-Semkow H. Protein Laboratory University of Copenhagen, Denmark

L a b o r a t o r y o f D e v e l o p m e n t a l
N e u r o p a t h o l o g y

- Dąbska M. State Institute for Basic Research in Mental Retardation, New York, USA /long term visit/
- Kozłowski P. Institute for Basic Research in Mental Retardation, New York, USA /long term visit/

Department of Neurochemistry

- Broniszewska-Ardelt B. Department of Neurochemistry, Purdue University, West Lafayette, Indiana, USA /long term visit/
- Khachatryan L. Laboratory of Preclinical Pharmacology Saint Elizabeths Hospital National Institute of Mental Health, Washington, USA /long term visit/
- Łazarewicz J. Institute of Zoophysiology University of Lund, Sweden
- Majewska M.D. Harvard Medical School Rap Lowell Laboratories Mc Lean Hospital Belmont, USA
- Pastuszko A. Department of Biochemistry University of Pennsylvania, Philadelphia, USA /long term visit/
- Rossowska M. Roswell Park Memorial Institute, USA /long term visit/
- Strosznajder J. Institut für Physiologische Chemie der Universität Köln, FRG
- Wideman J. Max-Planck-Institut Monachium, FRG /long term visit/
- Wróblewski J. National Institute of Mental Health, Laboratory of Preclinical Pharmacology, Washington, USA /long term visit/
- Zaleska M. Department of Pharmacology and Therapeutics State University of New York at Buffalo, USA /long term visit/

•

Department of Neurosurgery

- Jurkiewicz J. Neurochirurgische Klinik Kantonsspital Aarau, Swizerland /long term visit/
- Szewczykowski J. Memorial Sloan - Kettering Cancer Center, New York, USA /long term visit/

Department of Surgical Research
and Transplantation

Gałkowska H. Transplantation Division, Surgical
 Department University of Bonn, FRG

Grzelak-
-Puczyńska I. Norwegian Radium Institute, Oslo,
 Norway

Kupiec-
-Węgliński J. Surgical Research Laboratory Harvard
 Medical School, Boston, Mass., USA
 /long term visit/

Murawska M. Department of Surgery State University
 Groningen, Netherland /long term visit/

Ryffa T. Norwegian Radium Institute, Oslo,
 Norway

PARTICIPATION IN INTERNATIONAL SCIENTIFIC
MEETINGS IN 1981

Congress SEPCR "Occupational lung disease"; Göteborg, Sweden,
June 1-5

M. Głogowska, R. Romaniuk, M. Stereda-Przestaszewska

Conference of Presidium SEPCR, London, Great Britain,
January 28-30

W. Karczewski

XV Annual Meeting European Society for Clinical Investiga-
tions, Basel, Switzerland, March 19-21

K. Herbaczyńska-Cedro, K. Nazar

Seminar in Medicine, Tromsø, Norway, June 6-11

K. Herbaczyńska-Cedro

Catecholamines and the Heart, Munich, FRG, May 27-29

K. Herbaczyńska-Cedro

Conference on Cosmic Medicine and Biology - "Intercosmos",
Sofia, Bulgaria, June 4-9

S. Kozłowski

International Conference "Muscle in Sport", Utrecht,
Netherlands, March 23-26

K. Nazar

Symposium "Energy expenditure under field conditions":
Praha, Czechoslovakia, April 7-9
K. Nazar

German Society of Neuropathology and Neuroanatomy; Freiburg,
FRG, October 7-10
A. Kapuściński, D. Maślińska, M.J. Mossakowski

International Symposium on Stroke: Animal Models; Wiesbaden,
FRG, November 15-19
A. Kapuściński, M.J. Mossakowski

XIV Donau Symposium fur Neurologische Wissenschaften, Wien,
Austria, October 28-31
H. Kroh, M.J. Mossakowski, M. Ostenda

Symposium on Brain Aging; Berlin West, GFR, July 19-21
H. Kroh, M.J. Mossakowski

Congress Neuropathology and Psychiatry; Moscow, USSR, May 25
M.J. Mossakowski

Course for Young Neurosurgeons, Bratislava, Czechoslovakia,
August 0- September 5
L. Kuciński, R. Pluta

VI Meeting of the European Association for Cancer Research;
Budapest, Hungary, October 12-15
K. Domańska-Janik

72nd Annual Meeting American Society of Biological Chemists,
St. Louis, Missouri, USA
L. Khachatryan

8th Meeting of ISN; Nottingham, Great Britain, September 6-13
J. Łazarewicz, K. Noremborg, J. Strosznajder, T. Zaleska

Satellite Meeting "Phospholipid Metabolism in the Nervous
System"; Birmingham, Great Britain, September 12-16
J. Strosznajder

Symposium Reanimation Cerebrale; Lugano, Switzerland,
November 10-16
J. Jurkiewicz

Congress of the European Functional Neurosurgery and Stereotax-
y Society; Zurich, Switzerland, July 9-12
E. Mempel

Conference of Presidium European Society for Surgical
Research; Munich, FRG, January 31 - February 2
W. Olszewski

8th International Congress of Lymphology; Montreal, Canada,
September 20-25
B. Łukomska, W. Olszewski, M. Ruka