12 X-RAY-PROVOKED NON-MENDELIAN TRANSGENERATIONAL ONCODETERMINANTS

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Introduction

Cancer is the most important risk of radiation exposure. There is a definite lack of suitable test systems, human epidemiological data are only available for certain radiation types, especially not for charged particles. We use the Xiphophorus model [1] which is genetically well characterised. As a prelude to experiments with heavy ions we report here on results obtained with x-rays to establish the necessary baseline for future studies. Apart from this direct aim we hope to obtain also a better insight in the genetical determination of cancer formation.

The normal xiphophorine pigment cell pattern, i.e. the cellular basis on which melanoma develops, is determined by developmental genes (oncogenes) that are conducted by x-*erb*B*[a], a xiphophorine homolog of the erythroblastosis virus *erb*B oncogene (Zechel et al., 1988; F. Anders, 1991; [5],[2]). The oncogenes are negatively controlled by directly acting suppressor genes and positively controlled by indirectly acting oncostatic genes (F. Anders et al., 1985 [3]). Xiphophorine melanoma, like neoplasia in general, develops mainly following loss, impairment or malfunction of the controllers, and is boosted by endogenous or exogenous tumorpromoters (A. Anders et al., 1991 [1]). The oncodeterminants, in reality normogenetic developmental genes and their controllers, are inherited according to Mendelian rules (F. Anders and Zechel, 1993 [4]).

We are studying a so far unkown oncodeterminant which, following a single treatment of embryos or eggs with X-rays, generates a non-Mendelian transmission of melanoma and an accelerating increase of its incidence through the succeeding generations.

The results obtained although interesting have to be considered as preliminary. They will be supplemented by investigating lower doses and in the case of pregnant fish different stages of embryogenesis.

Materials an methods

Platyfish (*Xiphophorus maculatus*) exhibiting black spots on the body side (*Sp*) or a black spot at the dorsal fin (*Sd*), or stripes on the side of the body (*Sr*) were used. Mature fish were irradiated in a metal basin filled 2 cm with water. It was placed 80 cm from the focus of a Röntgen Müller apparatus MG 150. X-rays were emitted at a dose rate of 0.22 Gy/min, 150 kV, 12 mA and filtered through 0.2 mm Cu and 0.5 mm Al. Germ cells were irradiated in the parental individuals, embryos in pregnant females. For young and small fish which require a more gentle treatment we replaced the metal basin by cell culture flasks. The fish were silenced by cooling to 12 °C and - after the treatment - waken up by warming. Whole- body x-ray doses in the range of 1-15 Gy were used which did not cause significant lethality. Only surviving animals were included in scoring.

Results

Insensitivity of purebred adult platyfish to provocation of melanoma.
Whole body X-irradiation with 1 to 20 Gy which has been performed with several thou-

P.P.

sands of purebred adults for different purposes, has no detectable effect on the number of melanophores, as well as on spots and stripes that, in principle, may grow out to melanoma. This observation contributes to our so far indisputable findings that, based upon Mendelian genes, natural selection in the wild populations is directed against neoplasia and makes the animals largely insusceptible to neoplasia, i.e insentitive to carcinogens.

Sensitivity of germ line cells and embryos of purebreds to provocation of outgrowth of spots to benign melanoma in the development to adults.

Males, and females bearing eggs and embryos in their belly were treated with a single X-irradiation of 9 or 15 Gy, respectively. While this treatment does not impair the health of the parents and the offspring, and has no effect on the spot and stripe patterns of the parental adults, it causes - irrespective of whether eggs, embryos or both were hit - a uniform increase in the number of the spots and an enlargement of the spots to confluent and thickened areas in the developing generation. No such enlargement was observed in the stripes. A clear dose-effect relationship could not yet be established.

The enlarged spot areas resemble those of the wellknown benign melanomas which develop "spontaneously" in the platyfish-swordtail F1 hybrids and in those BC segregants, that harbor the oncostatic differentiation gene *Diff*. The genetic basis of the X-ray-provoked benign melanoma of the purebreds, however, is not identical to that of the hybridization provoked spontaneously developing benign melanoma: Matings between benign melanoma bearing F1 hybrids produce offspring exhibiting tumor expression from zero to extreme malignant whole-body melanoma. This result suggests a Mendelian inheritance of oncodeterminants. In contrast, the result of matings between the benign melanoma bearing purebreds grown up from irradiated germ line cells and embryos follows mechanisms other than Mendelian laws:

The nontreated adult offspring of the animals which had been treated as embryos or eggs in the belly of their grandmothers (9 or 15 Gy) exhibit benign melanomas like their directly treated (as embryos and eggs) parental generation. This enhancement of the tumorous phenotype remained unchanged without any further treatment through 45 inbred generations of two closed stocks. Since this increase takes place in all fish developing from the irradiated embryos and germ cells as well as in the descending generations, we conclude that both somatic and germ cells are hereditarily altered in the same direction by a so far unknown mechanism.

In order to examine more closely the genetics of the X-ray-provoked increase of phenotypic expression of the spots to benign melanoma, three types of crossing procedures were accomplished between nonirradiated platyfish carrying chromosomes that had been either irradiated or non-irradiated in the ancestry (Table 1; a,b,c):

a). Nonirradiated X^{Sp}-X^{Sp} females bred from purebred ancestors which were irradiated as embryos and, therefore, exhibit spot outgrowths to benign melanoma (the irradiated chromosomes are symbolized by conture letters in the table) were crossed with nonirradiated X^{Sp} Ymales bred from nonirradiated normal spotted purebreds (the nonirradiated chromosomes are symbolized by normal letters). Double reciprocal crosses with respect to sex and to the irradiated and nonirradiated ancestry were also made. These crosses resulted in similar increase of *Sp* expression irrespective of whether the descendants carry the irradiated or the non-irradiated X^{Sp} chromosome.

b). To distinguish the effects of irradiated and nonirradiated autosomes and X- and Y-chromosomes individually, nonirradiated females of *Sp* stocks bred from fish which were irradiated as embryos in the ancestry were crossed with nonirradiated males of *Sd* stocks bred from nonirradiated fish. Triple reciprocal crosses with respect to sex and the *Sp*-and

Figure 1: **Increase of tumor expression from spots to melanoma in descendents of crosses of nonirradiated animals carrying irradiated (9 or 15 Gy; contured symbols) and/or nonirradiated chromosomes (normal Symbols). 5 experimental sets each.** (A, autosomes; X, Y, sex chromosomes; Sp, spotted body side; Sd, spotted dorsal fin)

Genotypes of ancestral generations	No. of descendents	Tumor expression in the descendents
a. AA $\overline{X^{Sp}}$ $\overline{X^{Sp}}$ x AA X^{Sp} Y AA X^{Sp} X^{Sp} x AA $\overline{X^{Sp}}$ Y	several thousands in 35 generations	all animals exhibit increased *Sp*
b. AA $\overline{X^{Sp}}$ $\overline{X^{Sp}}$ x AA X^{Sd} Y	44	
AA $\overline{X^{Sd}}$ $\overline{X^{Sd}}$ x AA X^{Sp} Y	43	all animals exhibit increased
AA X^{Sp} X^{Sp} x AA $\overline{X^{Sd}}$ Y	124	*Sp* and *Sd* (n =304)
AA X^{Sd} X^{Sd} x AA $\overline{X^{Sp}}$ Y	93	
c. AA $\overline{X^{Sp}}$ X^{Sp} x AA X^{Sp} Y	91	normal to less increased
AA $\overline{X^{Sp}}$ X^{Sp} x AA $\overline{X^{Sp}}$ Y	54	normal to increased
AA $\overline{X^{Sp}}$ X^{Sp} x AA $\overline{X^{Sp}}$ Y	32	increased

Sd- chromosome from irradiated and nonirradiated stocks were made. All of these crosses reveal an increased expression from spots to benign melanoma in both irradiated and nonirradiated *Sp*- and *Sd*-phenotype in the male and female offspring (n= 304) to the same extent as observed in those parents having the complete set of irradiated chromosomes. Individuals inheriting both *Sp* and *Sd* phenotypes show outgrowths to benign melanoma in both. The results indicate firstly that the increase of *Sp* and *Sd* expression in the offspring is neither dependent on a specific mutation of the critical x-*erb*B^{*a} oncogene nor due to any other genetic change restricted to the irradiated X*Sp* or X*Sd* chromosome, secondly, that this genetic alteration cannot involve mutations of cytoplasmic constituents contributed in different quantities by ovum and sperm because the increase of phenotypic expression from spots to melanomas is independent of the sex of the parent contributing the irradiated chromosomes to the offspring, and thirdly, that half of the diploid chromosome set that is irradiated is as effective in the offspring as the entire irradiated chromosome set in the parents. The latter observation suggests a matching of the effect in the offspring up to that of the parents.

c). To test the distribution of the determinants of the increased *Sp*- and *Sd*-expression in the genome more closely, males and females having half of their chromosomes anchestrally irradiated, were crossed with fish having none of, half of, or the complete set of chromosomes irradiated. The result indicates that the variation of the phenotypic elevation of the spots to melanomas corresponds to the variation of the mode number of irradiated chromosomes in the offspring. This variation points to a large number of oncodeterminants that are widely distributed in the chromosomes. Nonchromosomal determinants cannot be involved in the increase of spot expression to melanoma because one would not assume that these are transmitted to the offspring in proportions similar to those of the

chromosomes.

The question arises whether the chromosomes treated in the ancestry of the platyfish carrying the benign melanoma outgrowth will intensify the well known ordinary benign and malignant melanoma that appears in the platyfish/swordtail hybrids "spontaneously" (see F. Anders, 91). Therefore, nonirradiated platyfish of the *Sp* and *Sd* stocks bred from fish irradiated as embryos 10 generations earlier, were crossed and backcrossed with nonirradiated swordtails bred from nonirradiated ancestors. Four sets of experiments produced benign melanoma bearing F1- and BC-hybrids (with *Diff*) and malignant melanoma bearing BC-hybrids (without *Diff*), and all of them (n=155) revealed an earlier onset and a boost of tumor severity as compared to the standard displayed by the ordinary Mendelian tumor determinants of the oncogene-suppressorgene machinery.

Tumourigenesis in hybrid fish: the "I-model"

The genotypes used so far are highly suitable for the detection of the transgenerational uniform augmentation of Mendelian-based melanoma development by the non-Mendelian oncodeterminants at the individual level; however, they are inadequate for the detection of Mendelian-independent tumor frequencies at the populational level that could mimic the mysterious increase of melanoma frequency in human populations. To study the putative influence of the transgenerational oncodeterminants at the populational level we developed a hybrid fish model in which all individuals are equally strong protected from melanoma by a particular critical suppressor gene which is closely linked to the x-*erb*B^{*a} oncogene. Both x-*erb*B^{*a} and the linked suppressor are the only platyfish-specific oncodeterminants in the swortail genome. The insensitivity to hybridization-conditioned Mendelian melanoma and the sensitivity to X-ray-induced melanoma in the model appear as different developmental processes. Insensitivity to hybridization of the *Sr* phenotype remains unchanged in the model, its insensitivity to X-rays, however, changes to sensitivity, and neoplasia can be provoked by mutations of the only Mendelian controller that is retained in the model. Because initiation is required for melanoma in this model we called it "I-Model". All individuals of the I-Model are equally endowed with the capacity to develop melanoma. The non-Mendelian transgenerational oncodeterminants which appear to be selfish are expected to turn the balance from non-tumorous to tumorous fish in a given experimental population (Table 2; a,b,c):

Thousands of fish of the I-Model have been bred. Generally they remain lifelong tumorfree. However, if the adults of the I-model were treated with X-rays (10 Gy/3 x 45 min, 6 intervals), 19% of the survivors (390/2010) developed malignant melanoma after 8 to 10 months. The sharply circumscribed shape of the melanomas suggests their somatic mutation-conditioned unicellular origin. We are planning to use this model in future studies both with x-rays and heavy ions.

We compaired also two successive siblings of one pair of parents each. The one siblings were born before, and the others after their mother was treated with X-rays. Melanoma formation of the treated animals starts developing early in embryonic life and may end lethally as wholebody melanoma at the time of birth. They are of unicellular origin like the irradiation-provoked melanomas in the adults although they look, due to their early appearence, large-faced like the common Mendelian ones that actually are of multicellular origin. An average 33 % of the adults treated as embryos develop severe melanoma. No Mendelian background of melanoma incidence was observed. Non-tumorous adults showed no signs of being cryptically affected by the treatment as embryos.

Figure 2: **Increasing X ray.initiated melanoma incidence running through the generations of the I-model as compared to the lack of increase in the promoter-promoted P-model (counted in adults of age 8-10 months).**

Treatment of	Melanoma in Adults			
	Initiation in the I-Model	%	**Promotion in the P-Model**	%
a. Adults	**390/2010 (589/3348)** # after 8-10 months; in the adults only	**19 (18)#**	**832/974** § after 8-10 weeks;	**85**
b. Embryos	**234/703** starting in the embryos	**33**	**0/218** §	**0**
c. Embryos in the 17th ancestral generation	**591/1131** starting spontaneously in the embryos of the descendent generations	**52**	**0/567** §	**0**

Total of data for treatment with X-rays, MNU, ENU, IQ; § Total of data for treatment with Methyltestosterone, Trenbolone, Stanozolol, Tamoxifen.

Non-tumorous mates of siblings treated as embryos were inbred in closed stocks. Tumorous offspring resembling those of the irradiated anchestry in shape and percentage occurred without any further treatment. As these tumorous fish occurred in the closed stock laboratory populations, they were excluded from their possible contributions to the succeeding generations. Selective decrease of tumor incidence which was to be expected was not observed. Instead, melanoma incidence increased in the populations of the closed stocks. Since the beginning of the irradiation/selection experiment 8 years ago we estimate an average run of 17 generations through the populations of the closed stocks of the I-Model. When the fish reach an age of about 20 months, they become more melanomatous, and additional sarcomas and carcinomas develop. At present the number of generations bred in the closed populations is estimated to 22, and no further change was observed. It appears that a balance between increase of tumor incidence and rate of tumor deaths stopped the endogenous populational dynamics, as if the phenomenon were epidemic.

In parallel to the phenomenological investigations studies at the molecular level are in preparation.

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(Heavy ion action on Deinococcus radiodurans cells in comparison to sparsely ioniszing radiation)
University of Köln, 1994

ENCLOSURE # 6

NEUROLAB

12th Joint NASA / DARA-DLR Life Sciences Working Group Meeting

Ames Research Center
Moffett Field, California
October 26-27, 1994

Mary Anne Frey, Ph.D.
Neurolab Program Scientist
LBSAD

PARTNERS

- UNITED STATES
  - National Aeronautics and Space Administration
  - National Institutes of Health
    - Division of Research Grants
    - National Institute on Aging
    - National Institute of Child Health and Human Development
    - National Institute on Deafness and Other Communication Disorders
    - National Institute of Neurological Disorders and Stroke
    - National Heart, Lung, and Blood Institute
  - National Science Foundation (Sensory Systems and Neuroscience Program)
  - Office of Naval Research

PARTNERS (Continued)

- INTERNATIONAL
  - Canadian Space Agency
  - Centre National d'Etudes Spatiales
  - Deutsche Agentur für Raumfahrt-Angelegenheiten
  - European Space Agency
  - National Space Development Agency of Japan

TEAMS, TEAM LEADS, AND PRINCIPAL INVESTIGATORS

- 34 Principal Investigators selected into definition
- 8 science teams formed to integrate science and to optimize use of resources
  - 4 teams with human investigations
    - Autonomic Nervous System
    - Sleep
    - Vestibular
    - Sensory, Motor, and Performance
  - 4 teams with animal investigations
    - Adult Rodent
    - Mammalian Development
    - Aquatic
    - Neurobiology
- Team integration facilitated by Team Lead and NASA Project Office

HUMAN INVESTIGATIONS

Autonomic Nervous System — Team Lead: Ron White

Principal Investigator	Affiliation	Experiment Title
Friedhelm Baisch	DLR, Institute of Aerospace Medicine, Germany	Artificial Neural Networks and Cardiovascular Regulation
Gunnar Blomqvist	University of Texas Southwestern, USA	Integration of Neural Cardiovascular Control in Space
Dwain Eckberg	McGuire Research Institute, Inc., USA	Autonomic Neuroplasticity in Weightlessness
David Robertson	Vanderbilt University, USA	Autonomic Neurophysiology in Microgravity

Sleep — Team Lead: Jim Kiley

Principal Investigator	Affiliation	Experiment Title
Charles Czeisler	Brigham and Women's Hospital, USA	Clinical Trial of Melatonin as Hypnotic for Neurolab Crew
John West	University of California, San Diego, USA	Sleep and Respiration in Microgravity

HUMAN INVESTIGATIONS

Vestibular — Team Lead: Wally Wolfe

Principal Investigator	Affiliation	Experiment Title
Bernard Cohen	Mount Sinai School of Medicine, USA	Spatial Orientation of the Vestibulo-Ocular Reflex
Gilles Clement	CNRS, College de France	Visual-Otolithic Interactions in Microgravity

Sensory, Motor, and Performance — Team Lead: Jacob Bloomberg

Principal Investigator	Affiliation	Experiment Title
Otmar Bock	Inst. for Space & Terrestrial Science, Canada	Visuo-Motor Coordination during Spaceflight
Alain Berthoz	CNRS, College de France	Frames of Reference and Internal Models
Philip Njemanze	Chidicon Medical Center, Nigeria	Visual Cortex Blood Flow in Perceptual & Psychomotor Tasks
Chuck Oman	Massachusetts Institute of Technology, USA	Role of Visual Cues in Spatial Orientation
Tracey Shors	Princeton University, USA	The Stress of Space Flight: Effects on Learning

ANIMAL INVESTIGATIONS

Adult Rodent — Team Lead: Mal Cohen

Principal Investigator	Affiliation	Experiment Title
Ottavio Pompeiano	University of Pisa, Italy	Effects of Microgravity on Gene Expression in the Brain
Gay Holstein	Mount Sinai School of Medicine, USA	Anatomical Studies of Central Vestibular Adaptation
Bruce McNaughton	University of Arizona, USA	Ensemble Neural Coding of Place & Direction in Zero-G
Scott Brady	University of Texas Southwestern, USA	Space Flight, Stress, and Neuronal Plasticity
Charles Fuller	University of California, Davis, USA	CNS Control of Rhythms & Homeostasis during Spaceflight
Muriel Ross	NASA Ames Research Center, USA	Multidisciplinary Studies of Neural Plasticity in Space

Aquatic — Team Lead: David Liskowsky

Principal Investigator	Affiliation	Experiment Title
Shiro Usui	Toyohashi University, Japan	Subcellular Calcium Regulation in Microgravity
Bruce Jenks	University of Nijmegen, Netherlands	Effect of Microgravity on Brain Differentiation
Barbara Chapman	Cal. Inst. of Technology, USA	Microgravity Effects on Developing Vestibular Afferents
Michael Wiederhold	Univ. of Texas, San Antonio, USA	Development of Vestibular Organs in Microgravity
Stephen Highstein	Washington University, USA	Chronic Recording of Otolith Nerves in Microgravity

ANIMAL INVESTIGATIONS

Mammalian Development — Team Lead: Bill Heetderks

Principal Investigator	Affiliation	Experiment Title
Tsuyoshi Shimizu	Fukushima Med. College, Japan	Postnatal Development of Aortic Nerves in Space
Kenneth Kosik	Brigham & Women's Hospital, USA	Neuronal Development under Conditions of Space Flight
Kerry Walton	NYU Medical Center, USA	Effects of Gravity on Postnatal Motor Development
Kenneth Baldwin	University of California, Irvine, USA	Neural-Thyroid Interaction on Skeletal Isomyosin Expression
Richard Nowakowski	Robert W. Johnson Med. School, USA	Reduced Gravity: Effects in the Developing Nervous System
Danny Riley	Medical College of Wisconsin, USA	Effects of Microgravity on Neuromuscular Development
Jacqueline Raymond	Universite de Montpellier II, France	Microgravity and Development of Vestibular Circuits

Neurobiology — Team Lead: Rose Grymes

Principal Investigator	Affiliation	Experiment Title
Ingrid Block	DLR, Inst. of Aerospace Med., Germany	Graviperception and Signal Transduction in Single Cells
Eberhard Horn	University of Ulm, Germany	Development of an Insect Gravity Sensory System in Space
Haig Keshishian	Yale University, USA	Effects of Spaceflight on Drosophila Neural Development

NASA PERSONNEL CHANGES

HEADQUARTERS

Frank Sulzman ..... Acting Deputy to LBSAD Division Director

Mary Anne Frey ..... Neurolab Program Scientist

Bill Gilbreath ..... JSC Space Station Office

Cindy Martin ..... Neurolab Program Manager

JOHNSON SPACE CENTER

Howard Schneider ..... Retired

Jerry Homick ..... Neurolab Mission Scientist

INVESTIGATORS WORKING GROUP MEETING
August 2-4, 1994

- Objectives
  - Introduction and orientation to NASA for Principal Investigators selected into definition
  - Working group meeting for teams to start integration of proposals

- Results
  - Crew time allocated to each team
  - PIs directed to submit draft copy of integrated proposal on October 1, 1994

TEAM LEAD MEETING
October 12, 1994

- Objectives
  - ARC and JSC Projects provided an overall assessment of their teams requested resources
  - Each Team Lead provided a status on their team's integrated protocols
    - Team Leads provided a status on
      - Functional objectives
      - Resources required to support these activities
        - Crew time
        - Subjects
        - Hardware
        - Rack space / Stowage volume
  - National Institutes of Health (NIH) Division of Research Grants (DRG) provided a description of Science Peer Review of the integrated proposals
    - Format for the Team Integrated Proposals
      - Protocols
      - Co-Investigators
      - Budget

TENTATIVE SCHEDULE

1994

November 5	Send PIs instructions for integrated proposals and revised budgets
Nov. 15 - Dec. 15	NASA meetings with partners on Neurolab budgets
November	Preliminary feasibility assessment analysis in progress by NASA Projects and Mission Science
December	Preliminary feasibility assessment to NASA Headquarters
Nov '94 - April '95	Experiment / Discipline Document

1995

Early January	Tentative Team Lead Meeting
January	Tentative Steering Committee Meeting (Dependent on preliminary Neurolab payload)
January/February	Investigators Working Group Meeting #2 (IWG #2)at KSC (Final version of integrated proposals due)
February	Payload Specialist Selection process starts
March	Integrated Experiments Requirements Document (IERD), Preliminary
March	NIH Science Review

TENTATIVE SCHEDULE (Continued)

1995 (Continued)

April	NASA Payload Recommendation Meeting
April	Steering Committee Meeting
Nov. '94 - April	Experiment / Discipline Document
May	NIH Council Meetings
May / June	Selection for Development (Recommend payload to NASA Associate Administrator)
May	Mission Science Requirements Document (MSRD), Preliminary
May	JSC Project Preliminary Design Review (PDR)
July 1	Start funding for development
July	ARC Project PDR
July	Timeline, Preliminary
August	IWG #3
September	Human Research Policy and Procedures Committee - Payload Protocols
November	Integrated PDR
Nov. - Jan. '96	JSC Mock-up Integration

TENTATIVE SCHEDULE (Continued)

1996

February	IWG #4
February	Projects' Critical Design Review (CDR)
February	Safety Reviews Phase 0/I (Flight and Ground)
February	Payload Crew Selection
March -Jan. '98	Crew Training
June	Integrated CDR
August	IWG #5
August	Orbiter Crew Selection
September	Safety Review Phase II (Flight and Ground)
October	Flight Hardware Delivery to JSC
December	Science Verification Testing
~~Dec. – Sept. '97~~	~~KSC Level IV Integration~~

TENTATIVE SCHEDULE (Continued)

1997

February	IWG #6
February	Safety Review Phase III, Ground
February / March	Hardware Delivery to KSC
Feb. - Nov.	Mission Integrated Training Simulation (MITS)
June	Safety Review Phase III, Flight
August	IWG #7
August	Science Readiness Review
Oct. - May '98	Baseline Data Collection
Sept. - Dec.	KSC Level III/II Integration
November	Flight Operations Readiness Review
Nov - Feb. '98	Joint Integrated Training Simulations (JIS)
December	Payload Readiness Review
Dec. - Feb. '98	KSC Level I Integration

TENTATIVE SCHEDULE (Continued)

1998

January	Launch Readiness Review
February	Neurolab Mission
March	Postflight Operations Review Report
August	6 Month Postflight Science Report
August	IWG #8

1999

February	Final Science Report / Meeting

ENCLOSURE # 7

German-CIS-Cooperation in Life Sciences

1. before 1992:

- 1978 Salyut 6: experiments in the frame of the INTERKOSMOS program (GDR) on the Soviet space station; German cosmonaut (Jähn)
- experiments in gravitational and radiation biology on reentry satellites

2. 1992:

- March ´92: German MIR ´92 mission with 13 Life Sciences Experiments; German cosmonaut (Flade)
- December ´92 / January ´93: BION 10; cooperative experiment in gravitational biology; experiments in radiation biology within the ESA frame

3. 1993:

- July ´93: cooperative experiment (HSD) during the French MIR mission

German-Russian-Cooperation in Life Sciences

4. 1994:

- MIR ´92 extension (cooperative experiments HSD, VOG, SUR, PSY)
- strong participation in the EUROMIR ´94 mission (11 experiments)
- CPK/CNES/DARA pre-/postflight study (1994 - 1996)

5. Present planning or considerations:

- participation in the EUROMIR ´95 mission (6 experiments)
- further MIR utilization, e. g. cooperative MIR ´96 (?)
- in addition, further utilization of reentry satellites

GERMAN EXPERIMENTS FOR EUROMIR '94 MISSION
- Status July 1994 -

Principal Investigator	Experiment Title
CARDIOVASCULAR SYSTEM	
Kirsch (U Berlin)	Fluid Shifts into and out of Superficial Tissues and Tissue Stability along Body Axis under Micro-g Conditions in Man
Gunga (U Berlin)	Effects of Changes in Central Venous Pressure on the Erythropoietic System under 1-g and Micro-g Conditions
NEUROPHYSIOLOGY	
Scherer (U Berlin)	Adaptation of Basic Vestibulo-Oculomotor Mechanisms to Altered Gravity Conditions
MUSCULOSKELETAL SYSTEM	
Zange (DLR)	Magnetic Resonance Spectroscopy, Imaging of Human Muscles, and Muscle Biopsy before and after Space Flight
ENDOCRINOLOGY and METABOLISM	
Drummer (DLR)	Fluid and Electrolyte Balance during Weightlessness and Possibilities of their Regulation
Riepl (U München)	Gastroenteropancreatic Peptides during Zero Gravity and their Possible Involvement in Space Motion Sickness
Strasburger (U München)	Non-Invasive Stress-Monitoring in Space Flight by Hormone Measurement in Saliva

GERMAN EXPERIMENTS FOR EUROMIR '94 (contd.)

- Status July 1994 -

Principal Investigator	Experiment Title
OPERATIONAL MEDICINE	
Gundel (DLR)	Circadian Rhythms and Sleep during a 30-Day Space Mission
Mittelstaedt (MPI Seewiesen)	Spatial Orientation and Space Sickness
RADIATION BIOLOGY	
Reitz (DLR)	Radiation Health during Prolonged Space Flight
Obe (U Essen)	Chromosomal Aberrations in Peripheral Lymphocytes of Astronauts

GERMAN EXPERIMENTS FOR EUROMIR '95 MISSION
- Status July 1994 -

Principal Investigator	Experiment Title
NEUROPHYSIOLOGY	
Dietrich (U München)	Differential Effects of Otolith Input on Ocular Lateropulsion, Cyclorotation, Perceived Visual Vertical, Straight Ahead and Tonic Neck Reflexes in Man
Markham/Scherer (USA/U Berlin)	Correlation of Eye Torsion Changes with the Time Course of the Space Adaptation Syndrome
ENDOCRINOLOY AND METABOLISM	
Drummer (DLR)	Non-invasive Monitoring of Drug Metabolism and Drug Effect During Prolonged Weigthlessness
MUSCULOSKELETAL SYSTEM	
Zange (DLR)	MR Spectroscopy and Imaging of Human Muscles and Bones Before and After Space Flights
RADIATION BIOLOGY	
Reitz (DLR)	Radiation Health during Prolonged Spaceflight
Obe (U Essen)	Chromosomal Aberrations in Peripheral Lymphocytes of Astronautes

Agreement on Scientific Cooperation between CPK, CNES and DARA

Goal

- Cooperation of the three partners in pre- and postflight investigations on Russian cosmonauts in the field of human physiology in 1994 - 1996.

- Using jointly the Russian facilities at CPK and special equipment provided by CNES and DARA for possible future space station implementation

DARA contribution to the scientific program

- determination of the human cardiovascular functional status
- evaluation of cardiovascular deconditioning and fluid shift phenomena
- evaluation of longterm physiological changes of muscle efficiency

Agreement on Scientific Cooperation between CPK, CNES and DARA (contd.)

DARA contribution to the equipment

MEDEX Diagnosis System consisting of

- Central Data Processing Unit
- Data Transfer Interface
- Laptop Control panel
- Basic Module (ECG, EMG, Temp. etc.)
- Impedance Module
- EEG Module
- NIR (Near Infra Red; peripheral blood flow)

Scientific Program at CPK

1994	MEDEX-System validation with LBNP and centrifuge protocol, tilt table and orthostasis test
1995 - 97	Pre- and postflight measurements of cosmonauts (6 equipages = 12 crew members)

Programmatic Aspects

Objectives

Manned spaceflight has been an important element of the German space program over the last decades (Spacelab System, Spacelab-/MIR-Missions, Ground Infrastructure).

Germany intends to maintain its leading role in Europe in the area of manned spaceflight.

Future manned space activities will be strongly oriented towards international cooperation, both in the area of scientific programs as well as in the area of space infrastructure.

Concept MIR '96

Detailed objectives of a cooperative MIR '96 mission are:

- Continuity of scientific programs
  - regular access to space between 1995 and the space station aera
  - maximization of scientific return by internationally coordinated programs in view of scarce mission opportunities
  - multidisciplinary research comparable to space station utilization

- Cooperation with international partners
  - strengthening of scientific cooperation
  - gain of experience in common system/payload operations including DARA, NASA, and RSA
  - effective utilization of scarce ressources

Concept MIR '96

- Preparation of space station utilization
  - preparation of user community for space station operations
  - test of operational interfaces between German and Russian systems
  - optimization of user services with regard to ground/orbit interactivity
  - strengthening of know-how and experience of user support centers

Cooperation principles

- exchange of scientific data for cooperative scientific programs
- common utilization of scientific equipment
- distribution of tasks for system-/payload operations as for space station operations
- no exchange of funds

Required STS Services

- flight of German astronaut aboard the shuttle (return only)
- stowage accommodation for samples

Mission Scenarios

- DARA proposal
  - launch of German astronaut with Soyus
  - mission duration onboard MIR for 2 - 3 month
  - return of German astronaut with Shuttle
  - prelaunch BDC in Star City, postflight BDC at KSC
- Constraining factor: max. 3 crew-members possible with 1 Soyus capsule docked to MIR, i.e. German and American Astronaut not feasible onboard MIR at a time (with one crew rescue vehicle).

- RSA proposal
  - 30 day mission with Soyus launch/landing; mission operations during crew exchange
    - Soyus TM 25: Nov., 1996
    - Soyus TM 26: Apr., 1997
    - Soyus TM 27: Aug., 1997
- Possible solutions for extended mission duration (> 30 days) with Shuttle involvement to be investigated

DARA	Scientific Program MIR '96	WS2

MIR '96 to be seen as multidisciplinary mission with experiments from

- Earth Observation
- Space Science
- Technology
- Research under Space Conditions

  – Life Sciences
    - Biology
    - Human Physiology
  – Materials Science

Being a manned mission, emphasis is on Life Sciences, especially on HUMAN PHYSIOLOGY

DARA

Scientific Program

MIR '96

- Human Physiology -

Research Area	Research Topic	Facility
Cardiovascular and Pulmonary Physiology	cardiovascular deconditioning, fluid shift, homeostatic regulation	MEDEX System HSD Tonometer PHYSIOLAB (CNES) RMS-II (ESA) MIR Ergometer (Russia) MIR LBNP (Russia)
Neurovestibular Physiology	graviperception and gravisensibility, vestibular-ocular interactions, neural integration and regulation, space adaptation syndrome	VOG Cognilab (CNES)

DARA

Scientific Program

MIR '96

- Human Physiology - (cont.)

Research Area	Research Topic	Facility
Bone and Muscle Physiology	Muscular structure and function, bone decalcification	NMR (Pre-/Postflight) Bone Densitometer (ESA)
Endocrinology and Metabolism	Hormonal regulation, immune system	Blood Collection Kit, Urine Monitoring System, Saliva Sampling Kit
Operational Medicine	Human performance, circadian rhythms	Computer, Questionaire

DARA

Scientific Program

MIR '96

- Biology -

Research Area	Research Topic	Facility
Gravitational Biology	signal transduction chain (graviperception-gravitransduction-graviresponse)	BIOLABOR D-2 components (e.g. incubators)
Radiation Biology	dosimetric mapping, radiation effects chromosomal aberration	Biostack Active Dosimetry Unit

DARA

Scientific Program

MIR '96

- Materials Science -

Research Area	Research Topic	Facility
Materials Research	Crystal growth of semiconductors, solidification dynamics of alloys, phase separation phenomena in miscibility gap systems	CSK-4 (CSK-1) GALLAR (Russia) KRATER (Russia) ZONA-3 (Russia) OPTIZON (Russia)
Physical Chemistry and Processing	Thermophysical properties of undercooled melts, critical point phenomena	CSK-4 ALICE (CNES)

DARA

Scientific Program
MIR '96

- Cooperation -

MIR '96 is proposed as a cooperative mission, from operational as well as scientific point of view.

—> Scientific cooperation appreciated with scientists from

- IBMP
- ZPK
- Other Russian Institutions
- CNES
- ESA
- (NASA)

DARA

Scientific Program

MIR '96

- Cooperation - (cont.)

—> Cooperative use of facilities from

- Russia (e.g. LBNP, Ergometer)
- CNES (e.g. Physiolab, Cognilab)
- ESA (e.g. Bone Densitometer, Respiratory Monitoring System)
- NASA (to be elucidated)

DARA

Scientific Program

MIR '96

- Cooperation - (cont.)

MIR '96 as German cooperative mission is to be coordinated with the complete MIR utilization scenario:

- Russian scientific activities
- EUROMIR '95
- Shuttle/MIR missions
  (e.g. utilization of ESA BIORACK)
- Cassiopeé (French MIR 7/96)

GERMAN MIR '96 (e.g. 10 - 12/96)

- French MIR '97 (?)
- EUROMIR '97 (?)

ENCLOSURE # 8

NASA-DARA WORKING GROUP
Ames Research Center
October 26-28, 1994

SMALL PAYLOADS

- PRIMARILY UTILIZES SHUTTLE MIDDECK LOCKERS FOR FLIGHT OPPORTUNITIES

- RESEARCH AREAS INCLUDE:
  DEVELOPMENTAL BIOLOGY
  National Institutes of Health- Rodent Series
    - 2-3 flights per year over five years, first flight 11/94
    - utilizes animal enclosure modules
    - workings toward mouse flights, first flight early 1996

  Aquatic Research Facility
    - joint agreement with CSA (50/50) for one flight, TBD for future opportunities
    - first flight planned for early 1996

  Closed Equilibrated Biological Aquatic System
    - joint agreement with DARA for one flight
    - first flight planned for mid-late 1997
    - hardware under fabrication by DARA

SMALL PAYLOADS (cont.)

PLANT RESEARCH and TECHNOLOGY

Plant Growth in Microgravity Series (PGIM)

- one to two flights per year
- utilizes new plant growth facility (PGF), which includes active environment and temp control
- first flight planned for early 1996

Microgravity Plant Nutrient Experiment

- plant nutrient delivery system porous tube technology flight planned for early 1996

Chromosomes and Plant Cell Division in Space Series (CHROMEX)

- Flown five times to date, mostly reproductive studies
- anticipate to be less active with start-up of PGIM series, because utilizes less advanced Plant Growth Unit (PGU)

SMALL PAYLOADS (cont.)

HUMAN FACTORS

Human Performance Series (HP)

- First flight planned for early 1996 focuses on the stability and accuracy of cognitive and psychomotor performance across work shifts
- one to two flights planned per year

CELLULAR RESEARCH

National Institutes of Health Series - Cells

- two to three flights per year over five years
- musculoskeletal cell studies undertaken for five flights
- first flight occurred in April 1994
- utilize Space Tissue Loss hardware developed by the Walter Reed Army Institute of Research (automated cell culture system)
- second flight scheduled for November 1994, examines in-vitro calcification, and effects of space on skeletal Myofibers

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SMALL PAYLOADS (cont.)

ACROSS DISCIPLINES

Biological Research in a Can Series (BRIC)

- simple, passive petri dish container, which can be terminated with GN2 freezing
- one to three flights planned per year, not dedicated to a particular research area
- has flown twice, from gypsy moth larvae to starch concentration

Simplex

- centrifuge/incubator which utilizes Type I containers
- planned to be flight ready mid 1995
- hardware under fabrication by DARA

FUTURE ACTIVITY (Space Station ERA)

- EXPRESS RACK payloads, which are drawer size, or middeck size payloads will be flown in a rack dedicated to quick turnaround payloads, such as those in the small payloads program

SMALL PAYLOADS (cont.)

DARA SMALL PAYLOADS PARTICIPATION

- Will provide hardware details on the following for submission to the division wide NRA to solicit science utilization
  - SIMPLEX
  - GN2 Insert (test tube adaptability)
  - Cell culture containers (simple initiation/termination systems used on D2)
- One flight of CEBAS with Wiederhold and Blum projected for mid-late 1997
- Possible small payload flight candidate - I. Block (DLR) for BRIC flight planned for mid-late 1995

ENCLOSURE # 9

CO_2 STUDY AT DLR

Presentation to

12th Joint NASA/DARA-DLR

LIFE SCIENCES WORKING GROUP MEETING

Ames Research Center

Moffett Field, California

October 26-27, 1994

Mary Anne Frey, Ph.D.

Program Manager

LBSAD

CO_2 STUDY AT DLR
PURPOSES

- Learn the effect of moderately elevated CO_2 levels on human physiology as a guide for setting CO_2 limits for the Space Shuttle, Spacelabs, and International Space Station
- Understand the impact of elevated levels of CO_2 that occur in Mir on human physiology

CO_2 STUDY AT DLR
INVESTIGATIONS

- **CIRCADIAN RHYTHMS**
  - **PARISI**
    - Effects of CO2 on the circadian system, sleep, and respiration
  - **GUNDEL**
    - Sleep regulation and circadian rhythmicity during exposure to elevated CO2 levels
  - **SAMEL**
    - Circadian rhythms and stress under different CO2 concentrations and confinement conditions

CO_2 STUDY AT DLR
INVESTIGATIONS (CONT.)

- **METABOLISM**
  - **NOTH/KRASNEY**
    - Effects of sustained low-level elevations of CO2 on cerebral blood flow and autoregulation of the cerebral vasculature in humans
  - **STROHL**
    - Low-level CO2 effects on dead space, gas mixing, and closing volume
  - **DRUMMER**
    - Effect of elevated CO2 concentration on calcium, sodium, and water metabolism
  - **HOFFMAN**
    - Effects of a long-term CO2 exposure on parameters of physical fitness

CO_2 STUDY AT DLR
INVESTIGATIONS (CONT.)

- **PERFORMANCE**
  - **MANZEY**
    - Effects of CO2 on cognitive, psychomotor, and time-sharing during confinement
  - **TUROWSKI**
    - Effect of elevated CO2 levels on frontal Theta rhythm during task performance

CO_2 STUDY AT DLR
SCHEDULE

• READINESS REVIEW	10/6
• START BASELINE TESTING	10/17
• START 0.7% CO2 EXPOSURE	10/19
• END 0.7% CO2 EXPOSURE	11/11
• POST-CHAMBER TESTING	11/18
• DATA ANALYSIS	11/19-12/14
• MEETING TO DISCUSS RESULTS	12/15
• SECOND CHAMBER STUDY	Early '95

CO_2 STUDY AT DLR
TOPICS FOR DISCUSSION

- Tax on NASA payment to DLR

ENCLOSURE # 10

DATA ARCHIVE STATUS AND PLANS

R. J. White

SPACELINE

SPACELINE: AN ONLINE BIBLIOGRAPHIC DATABASE IN THE SPACE LIFE SCIENCES

- Cooperative Activity of the Life and Biomedical Sciences and Applications Division of NASA and the National Library of Medicine. Analogous to MEDLINE.
- Consolidates the results of the growing body of space life sciences research into a single, accessible resource, and enhances dissemination and visibility of this research to the space life sciences community, the broader scientific and educational communities, and the public
- Initial online database consists of a subset of NLM databases, from 1966 to the present, and NASA references of recent (1992-95) publications, primarily of investigators supported by NASA. When mature, SPACELINE will include both U.S. and international publications, reporting flight and ground-based research across the spectrum of space life sciences subject areas, from 1961 onward.
- Accessed via direct searching, which requires some familiarity with NLM searching, or via NLM's Grateful Med software, an interface that provides easy-to-use, inexpensive access to the literature

Schedule

- Fall 94: creation of SPACELINE prototype; begin transferring NASA data to NLM
- Early-mid 1995: database testing by volunteer testers
- Fall 1995: target date for first online availability

LIFE SCIENCES DATA ARCHIVE

Goal

- To develop a method for archiving and distributing results of space life sciences research sponsored by the NASA Life and Biomedical Sciences and Applications Division

Purposes of the Archive

- To increase the effectiveness of space life sciences data management in order to maximize the science output from these missions
- To provide a central repository of space life sciences data
- To provide researchers, educators, students and the general public with better access to life sciences information and results
- To provide access to data and information for future experiment planning and retrospective data analysis

Approach

- Existing assets are utilized
- Data from a particular mission are archived at the major data collection centers (ARC, JSC, KSC)
- Existing computer systems and user support services of the National Space Sciences Data Center (NSSDC) are used as the initial computer entry point for users
- Detailed information and data for each experiment are archived on CD-ROM by the appropriate NASA data collection center
- Activities of these existing facilities are coordinated at a NASA life sciences central node
- Central node also develops a mission CD-ROM product, which contains an overview of all the experiment data archived for a particular mission

Schedule

- December 1994 — Delivery of prototype system to NASA Headquarters
- Jan. - Oct. 1995 — Evaluation of prototype by potential user groups
- October 1995 — SLS-1 information will be available to all users
- 1997 — Fully operational, multiple-mission archive

ENCLOSURE # 11

CARDIOLAB

CNES/DARA COOPERATION IN CARDIOVASCULAR RESEARCH

- DARA and CNES are involved in the development of facilities dedicated to the exploration of the cardiovascular system of astronauts with mainly two hardware systems:

  - MEDEX (DARA)
  - PHYSIOLAB (CNES)

- A thorough analysis of the functional aspects reveals that the approaches are absolutely complementary.

- On these bases, DARA and CNES decided to put together their respective competencies with the goal to develop a new hardware, CARDIOLAB, for its use on the future International Space Station. As preparatory and accompanying steps, an extensive cooperative program in cardiovascular research on ground and in space is planned.

- The scientific goals of this approach are the following:

  - to study the adaptation of the cardiovascular system to microgravity

  - to guarantee to the crew members a high level of safety from the point of view of operational medicine (prevention and diagnostics).

CARDIOLAB

CNES/DARA COOPERATION IN CARDIOVASCULAR RESEARCH

The following functions are assumed to be performed by CARDIOLAB:

- the basic cardiovascular parameters: simple ECG, systolic and diastolic blood pressure, respiratory activity signal, skin temperature, EMG signal,
- longitudinal impedance measurement and profile electrical impedance tomography,
- regulation of human peripheral micro-circulation,
- electro-encephalography signal (EEG),
- hours ECG and blood pressure,
- continous blood pressure,
- venous compliance (plethysmography) and muscle tone,
- peripheral resistance (femoral, cerebral and aortic).

CARDIOLAB

CNES/DARA COOPERATION IN CARDIOVASCULAR RESEARCH

COOPERATION IN THREE PHASES

- **Cooperation in ground studies**

- Teams of German and French scientists will jointly participate in bedrest studies planned by CNES in 1995 and 1996.
- Between 1994 to 1996, investigations of physiological parameters of Russian cosmonauts during pre- and post-flight periods will be performed in the frame of a trilateral cooperation between DARA, CNES and CPK.

- **Cooperation on board of MIR station:**

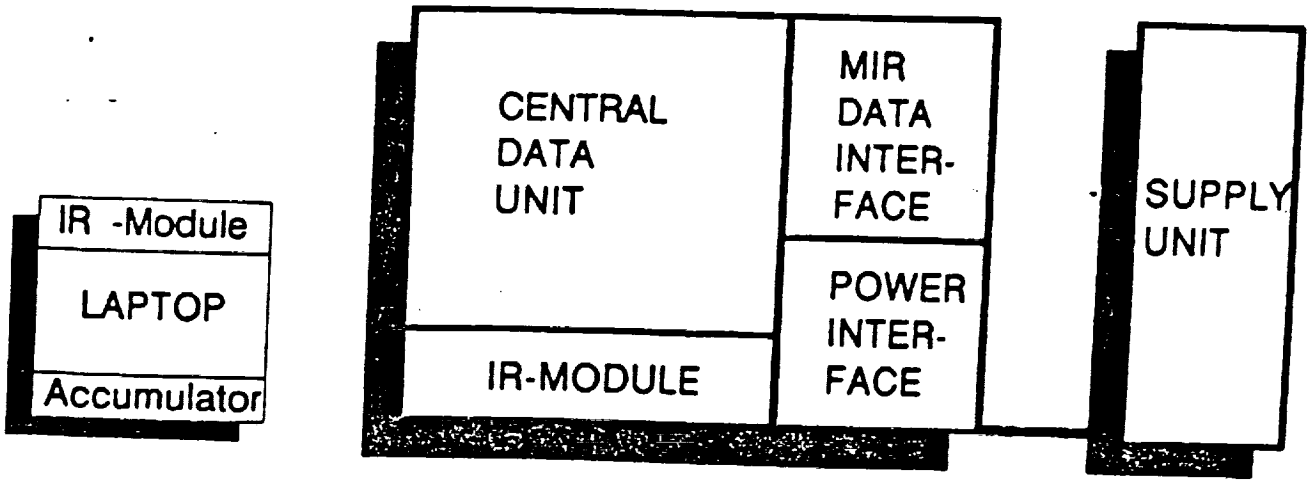
- The first utilization of the CNES PHYSIOLAB in space will be during the French MIR '96 mission Cassiopee. The first utilization of MEDEX is foreseen in a German MIR '96 mission. Also, the Cassiopee PHYSIOLAB hardware will be available for a German MIR '96 mission in exchange for implementing French experiments.
  Vice-versa, CNES may use the German MEDEX hardware for a planned French MIR 97-98 and implement German experiments.

- **Cooperation for Space Station:**

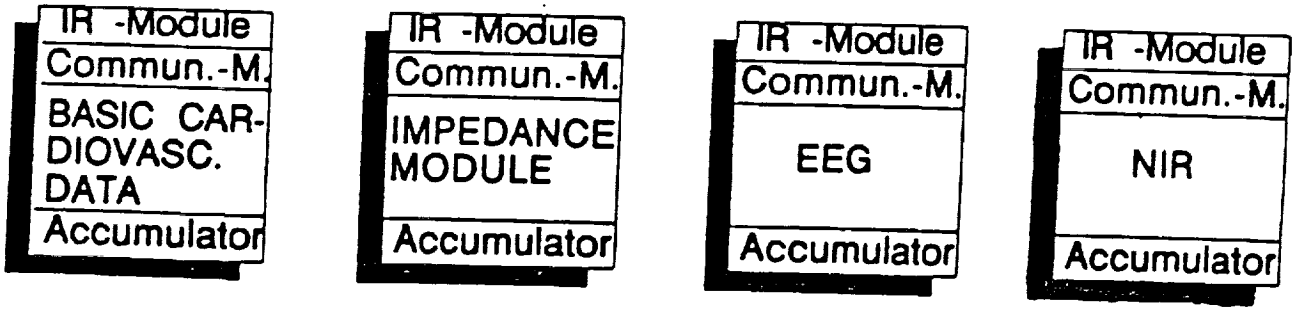
- Based on the MEDEX and PHYSIOLAB experiences, CNES and DARA will jointly develop a common facility for cardiovascular research for its use aboard the International Space Station, the CARDIOLAB.

Concept of MEDEX

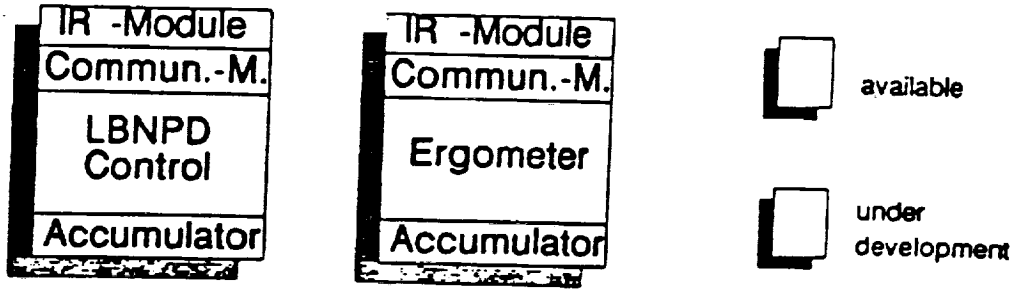
Human Physiological Data Acquisition and Diagnosis System



Measurement modules



Stimulation devices



CARDIOLAB Configuration

Physiological Parameter	PHYSIOLAB component	MEDEX component
blood pressure	Portapress	
respiratory rate		Basic Module
temperature		Basic Module
ECG	Holter	Basic Module
EEG		EEG Module
arterial resistance	Portable Doppler	
venous compliance	Plethysmogr.	
muscle tonicity	Reflexometer	Imp. Module (BIM)
fluid distribution by body impedance		Imp. Module (EIT)
fluid distribution by tomography		NIR Module
microcirculation		
blood/urine analysis	(CNES study)	(DARA)
stimulation devices	(CNES)	(DARA)
data acquisition	(CNES)	

MEDEX - Schedule

Laboratory Model I	Delivery and functional test	18. Oct. 1994
Laboratory Model I	Delivery to ZPK, Moscow	24. Oct. 1994
	CNES/DARA Experimenter /Coordination Meeting for Pre-postflight Studies at ZPK	24./25. Nov. 1994
Laboratory Model I	Verification phase at ZPK	Nov. - Dec. 1994
Laboratory Model II	Manufacturing	15. Oct. 1994 - 31. Jan. 1994
Laboratory Model I	Pre- and postflight investigations at ZPK	6 Missions/Equipages i.e. 12 Cosmonauts

Lab. Model I

Central Unit with Data Interface Supply Unit

Mobile Terminal

Basic Module

Impedance Module

EEG Module

Lab. Model II

Central Unit with Data Interface Supply Unit

Mobile Terminal

Basic Module

Impedance Module

EEG Module

NIR Module

LBNP Control

Leg Ergometer

DARA

ENCLOSURE # 12

12TH JOINT NASA/DARA-DLR LIFE SCIENCES WORKING GROUP MEETING
OCTOBER 26, 1994

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12TH JOINT NASA/DARA-DLR LIFE SCIENCES WORKING GROUP MEETING
OCTOBER 27, 1994

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