Annex V

FIFTH COORDINATION MEETING OF WHO COLLABORATING CENTRES IN RADIATION EMERGENCY MEDICAL PREPAREDNESS AND ASSISTANCE, (REMPAN)

Paris, France , 5-8 December 1994

Some Individual Contributions of Participants

Contents

BENEDICT

SFRO: Société Française de Radiothérapie Oncologique

34 TBI centres - 600 pt/yr

National registry of total body irradiation physical clinical and therapeutic database

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Bien	**A**dequate
Enregister les	**R**ecord of
Nombreux	**M**any
Evénements	**E**vents
Des	**I**n
Irradiations	**T**otal
Corporelles	**B**ody
Totales	**I**rradiation

TBI and time dose factors

Total dose
Fractionation
Elapsed time

Total Dose

- Monitor dose: midplane at L4 level
- Volumes of interest at Tenon
  - Mediastinum
  - Lung (right or left)
  - Brain
  - Liver

Dosimetry at Tenon Hospital

- Monitoring with 5 pairs of semi-conductors (opposed anterior and posterior)
- Thermoluminescence by LiF
- Dose at midplane of each volume

BENEDICT

- Dose at midplane of each declared volume
- Direct connection with diodes (DPD510)

TIME FACTORS

1. Dose increments (I)
2. Exposures (E)
3. Fractions (F)
4. TBI

1 - INCREMENT OF DOSE (I)

Any elementary fraction of uninterrupted exposure irradiation during which all parameters are unchanged .

- patient's position
- beam balistics
- interposition of blocks...

Only the duration of irradiation may change

INTERVAL BETWEEN TWO INCREMENTS (In)

Unexpected

Due to .

- patient : nausea, vomiting...
- personnel : drug administration, position control
- machine breakdown
- dosimeter ' incident

Any time the beam is "off"

2 - EXPOSURE (E)

- Consists of one or several dose increments
- Conditions of exposure are prescribed
  - dose at midplane at L4 level
  - beam : direction, size, attenuators
  - patient position
  - shielding
  - volumes of interest

INTERVALS BETWEEN EXPOSURES

- Planned from 10 to 20 min
- Changes in beam set up
  in patient position
- Biological effects and recovery

3 - FRACTION (F)

Made of several successive exposures during the same course of TBI

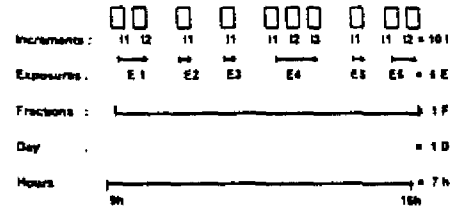
INTERVAL BETWEEN FRACTIONS

- From 4h (day) to 18h (night)
- Biological effects and recovery

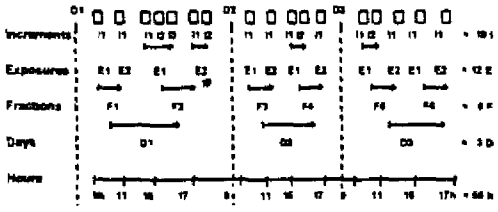
4 - TREATMENT (TBI)

Made of one or several fractions
Single-dose TBI = one fraction
Fractionated TBI = several fractions over several days

"MONO"FRACTIONATED TBI



HEXAFRACTIONATED TBI



TIME DOSE FACTORS : Tenon Hospital

	Dose (Gy)	Increments	Exposures	Fractions
Single TBI	10 Gy	⩾ 6	6	1
Fractionated TBI	12 Gy	⩾ 12	12	6

DOSE RATE : TWO SI UNITS

Absorbed dose	gray (Gy)
Time	second (s)
dose rate	Gy/s mGy/s
also	Gy/min, mGy/min
or	cGy/min
ex	rad/min

MEDICAL TBI

X-ray / gamma

Hematological malignancies / cancer
Prescribed chemotherapy before TBI
Other medical treatments
(anti-emetics, steroids)
Planned bone marrow transplantation

ACCIDENTAL WBI

Beta, gamma, X-ray

Healthy workers
or population

BENEDICT

- TBI techniques
- Patient
- Monitoring of TBI

COMPUTERS

Computer	Compatible IBM
Processor	386 or +
RAM	≥ 2 Mo
HD	≥ 40 Mo

SOFTWARE

Program	Clipper 5.0
BENEDICT	Executable installed on your computer

Tenon Hospital TBI TECHNIQUES

Beam	Fraction	Dose rate	Dose to L4/lung	Chronology of lung shielding
Alcyon 200	1	High	(10-08) Gy	1-2-9-10
Alcyon 250	6	low	(10-06) Gy	3-4-9-10
Linac (6MV)			(12-09) Gy	5-6-11-12
				5-6-9-10
				7-8-11-12
				3-4-7-8
				1-2-5-6
				1-2
				2-3
				3-4

From 1980 to 1994 : patients = 695
techniques = 21 different

PATIENT

- Pre TBI : - Administrative chart
  - Disease
- BMT
- Post TBI : Early follow up
  Late follow up

(SFGM)

MONITORING OF TBI

- paper
- computer + manual entry BENEDICT
  => exposure level
- computer + on line acquisition
  => automatic recording in BENEDICT at each increment level

DURATIONS OF FRACTIONATED TBI

	10h	11h	15h	16h	per day	3 days
	☐	☐	☐	☐		
Dose per exposure	1 Gy + 1 Gy		1 Gy + 1 Gy		4 Gy	12 Gy
Duration of exposure	20 min		20 min		40 min	120 min
Duration of fraction	60 min		60 min		120 min	360 min
Duration of daily treatment					6h	18h
Duration of TBI						54h

DOSE RATES IN FRACTIONATED TBI

	Instantaneous	Average
During exposure	0,8 mGy s^{-1}	0,80 mGy s^{-1}
During fraction	0,8 mGy s^{-1}	0,55 mGy s^{-1}
During a day	0,8 mGy s^{-1}	0,18 mGy s^{-1}
During TBI	0,8 mGy s^{-1}	0,07 mGy s^{-1}

CONCLUSION :

WHAT CAN WE LEARN FROM MEDICAL TBI ?

1. Nothing ?
2. Tolerance during TBI
   - vomiting after 2 or 3 Gy
   - action of Ondansetron, Granisetron, etc.
3. Biological changes at various dose/time factors
   ⇒ blood or exhaled air samples .
4. Theoretical models of stem cell circulation
5. Recording of dose time factors is an investment for future studies

MEDICAL TBI vs ACCIDENTAL WBI

Dose distribution	homogeneous ± 5 % (lungs)	not homogeneous
Dosimetry Quality	excellent	approximate
Radiation Quality	known Co 60 4 to 25 MV	from Goiana Cs to Tchernobyl mixture
Dose rate	instantaneous vs average (fraction, day, TBI)	"flash" continuous variable

The plan of annual obligatory investigation was for revealing of stochastic and non stochastic effects of irradiation of these cohorts. The estimation of homeopathic, immune, nervous and endocrine systems activities was of extreme interest. The realisation was shown on three main levels (slide):

Level	
I - Screening	- district, region, state level with the respect of inhabitance place
II - Qualified study	- region ;and state level
III - Expert level	- region and state level

Chernobyl accident irradiated population registry hierarchy

Expert level Region and state	State
Qualified study District, region and State	Region, State level
Screening	District, Region, State level

Database has given the possibility of integral estimation health condition of different cohort of victims after accident.

Since 1987 ware determined methods of clinical investigation of patients, who were undergone to irradiation. There were divided on clinical and clinical and laboratory methods. Clinical methods include the obligatory investigation of different physicians (slide):

- therapeutits - radiologist
- haematologist
- endocrinologist
- neuropathologist
- dermatologist
- ophthalmologist
- paediatrics
- psychiatric
- gynaecologist

The consultation of otolaryngologist and urologist is done if somebody need. Clinical and laboratory methods were divided on obligatory and special.

Haematological and others methods that are used in Region and State Level and Institute of Clinical Radiology of Scientific Centre of Radiation Medicine (slide)

Obligatory	Special
peripheral blood analysis	bone marrow investigation
biochemical blood analysis	cytogenetic investigation
hormone blood analysis	coagulation investigation
immune blood analysis	serum lipid investigation
urine analysis	serum phospholipid investigation
Ultra scan investigation of internal organs	urine glucose investigation
Ultra scan investigation of thyroid gland	bacterial investigation of biological material
ECG	Electroencephalography
Reovasographia	Vestibulomethry
Endoscopia of gaster, colon	X-ray investigation of different organs
	lung functional investigation
	spyrometric stress test on cycle ergometer
	Thermography

The investigation of blood hormones includes the determining of T_3, T_4, ACTH, insulin, cortisol, prolactin, LH, FSH, testosterone, oestradiol.

Immunological investigation is include the determining of:

*T-CELLS:	(1)	CD1+	CD2+3-
	(2)	CD3+	CD4+8+
	(3)	CD3+	CD3+HLADR-
		CD4+8-	CD4-8+
		CD4+Leu8+	
	(4)	CD3+HLADR+	CD3+16+56+
*B-CELLS:		CD10+ CD19+	CD22+ CD23+
		CD3-HLADR+	Surface IG+
*NK-CELLS:		CD8-57+	CD3-16+56+
*MONOCYTES:		CD14+	HLADR+

We kept the clinical information on paper till 1990. From 1990 we began the information transformation in computers. Since 1991 till 1994 there were created several databases for endocrinological, haematological, immunological and others investigations, and local database for

patient after ARS and their social data. As a rule we used such programmes as FoxBase and FoxPro 1.0-2.0.

Since 1993 we has begun the investigation in frameworks of JSP3. It's program includes the elaboration of database for acute period of ARS and follow up as an International database. The first part of investigation was performed under leading of professors T. Fliedner and A. Baranov. For second part of work the questionnaire was created by Ulm and Moscow groups. It have to be the basis of this second part. The results of this work were reported in Paris in Nov. 1993 and in June 1994 in St. Petersburg. The Kiev group start its collaborated work in 1994 We suggested some prepositions for improving of questionnaire that it can match for our investigation. The workshops in February and June 1994 in Ulm and in Maz 1994 in Kiev allowed us to determine the database structure. Using the Microsoft program Access we created the main tables and forms for begin fulfilling.

As we mean, the next steps have to be done in follow directions:

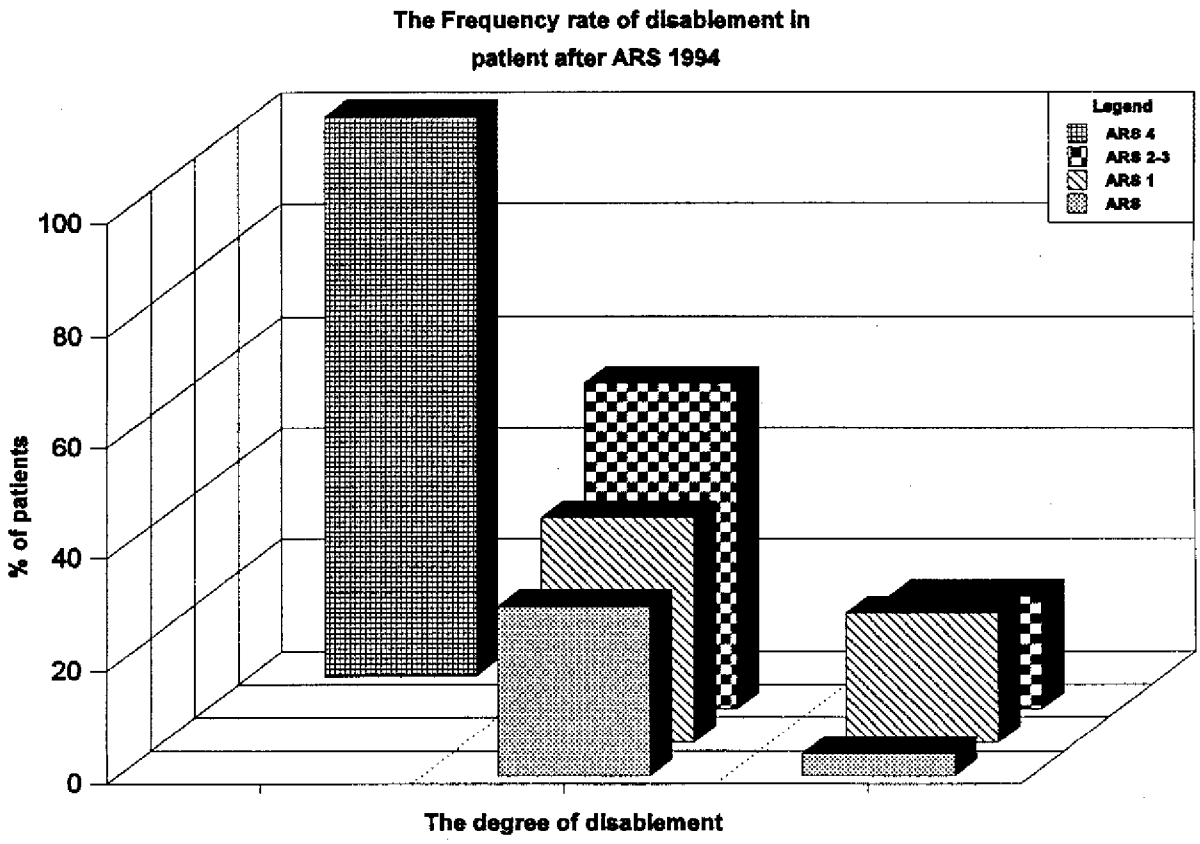
1) To determine the unique program for all collaborators;
2) To determine the unique structure of database;
3) To transform information from paper to computer with parallel it keeping in special paper forms.

The patient after ARS data about haematoimmunological and endocrinological homeostasis and functional state of internal organs are more interesting in connection of radiation promote consequences.

During eight years period of observation in 40% of persons with ARS in anamnesis we registered the disorders of haemopoiesis such as transient and stable leucopenia and leucocytosis. In 1993 patient after ARS III died from erythromyelodisplastic syndrome. The others reasons of death are represented on next slide().

Name	ARS	Year of death	Reason of death
1. Nimchencko G.F.	0	1986	Automobyl accident
2. Gorodetskiyi R.A.	0	1987	Hypoplasia of Haematopoiesis
3. Voronenko V.Y.	2	1987	Gangrene of lung
4. Tremin V.A.	0	1988	Organic disease of brain and spinal cord
5. Climenko Y.F.	2	1990	Coronary heart disease
6. Vlasenko M.P	3	1992	Coronary heart disease
7 Krisko M.F.	0	1993	Sarcoma of thigh
8. Pritshepa V.A.	1	1993	Coronary heart disease
9. Busigin G.V.	3	1993	Myelodisplastic syndrome
10.Turovets V V.	0	1994	Coronary heart disease

The somatic status in individuals who suffered ARS in period after accident characterized of many chronic diseases. There was determined the tendency to increase of digestive tract diseases (slide 6 A.N.), to increase and following decrease the level of respiratory system disease (slide 7 A.N.).



The frequency of psychoneurological disorders such as syndrome of vegetative disfunction, asthenic, psychoastenic and cerebropathic conditions have the tendency to decrease in comparison to 1986 year (slide 8 A.N.). Nevertheless 5-6 years later the accident in many patients there was the tendency to transformation this disorders to organic neurovascular pathology (arterial hypertension, discirculatory encephalopathy, psychoorganic syndrome with change of personality).

The frequency rate of cardiovascular system increased (slide 9 A.N.). There was revealed the decrease of physical work capacity which was more strong in group of patients after ARS II-III (slide 10 A.N.).

It was connected with increase of cases with pathological types of responses during cycle ergometry which correlate with dose of radiation.

Mental capacity measured on sensomotor and abstract-logical activity's models was decreased simultaneously with the degree of radiation damage. It combines with understating their own mental capacity and absences and efforts and risks for success achievement.

The decrease of physical and mental working capacity and concrete pathology of different organs and systems caused growth the number of patients with disablement. At present time almost all patients after different degrees of ARS have the second group of disablement (slide).

In one third of patients quantitative and qualitative changes of immunity were seen including T-suppressor cell decrease and serum IgG and IgM disrepansies.

An E-receptor percentages and thermostability, CD3+, CD4+ receptors expression and CD4+/CD8+ ratios decrease were seen in radiation induced immune deficiencies. Further investigation showed the decrease of antigen expression associated with helper/inducer function, mitogen response and activation of pan-B b B-blast activation antigens expression (CD3Dr-; CD4+8-, CD22+, CD23+). None of changes were seen in CD4-8+ b CD8+57- cells content. In CD57+8-cells a tendention to normalization was detected in the 48 months period.

Computer database studies allowed us to show the dose-effect and medical involvement dependencies. Three groups of patients were divided in the period from 48 to 66 months after the irradiation- persons with normalisation of immune system parameters including CD3+, CD4+ percentage, CD4+8+, cells increase (21.3%), persons with constant lymphocytosis and monocytosis and Charcot changes of CD3+Dr-, CD4+8- cell content, dysimmunoglobulinemia with elevated CD4+ cell count (42/6%). In the rest of patients variable changes of Leu4+Dr-, Leu4+12- b Leu4+11-19+ were associated with leu4-Dr+, Leu4-12+, slg+, Leu3a+2a, Leu3a+8- cells decrease and selective and mixed immunoglobuline deficiencies increase. Dose-effect dependencies were seen in Leu4+Dr- b Leu3+2- cell content.

Activated cells studies showed a IL-2 CD25+ alpha-chain receptor and CD71+ cells increase.

Forming of radiation pathology is associated with immunogenetic factors:
the presence in HLA phenotype of antigens A10; A28; B16; B38; B35; DR3, DR4; phenotype Hp2-2, is associated with increased sensibility to radiation; the presence of specific of B15; A3; B7 - performed the protective function.

Dependence of clinical symptoms of ARS from a radiation dose is fenotypical caused, and reliability association threshold for immunogenetic markers is increased.

Antigen systems of erythrocytes (ABO, Rh-Hr, MNSs) compete with HLA-antigene's determinants, decreasing risk degree of realization of genetical predisposition to progress of pathological process for radiation, that can testify about the presence of functional relations between the elleleys and confirm the known theory, that antigens of erythrocytes system can modify the tolerance of organism in the environment

In the end of the analysis of our studying result of a role of immunogenetical structures of blood for forming of postradiation effects on the level of immune status of a human organism with assumption of tricky relations among the functional, as well as among genetical system, we have all of reasons to conclude, that for influence of radiation on a human organism, immune system is genetically determinate for support of immune homeostasis

In hormonal status cortisol level was increased during 1987-1993 and it is the evidence of effort of hypophysis-adrenal cortex adaptation system (slide 1 A.N.).

From 1991 to 1992 on background of progressive increase of cortisol level there was considerable decrease of corticotrophin concentration (slide 2 A.N.) that was increase of peripheral link effort and decrease of central link activity of hypophysis-adrenal system.

There was the weakening of testicles' androgen function on every stage of observation (hypotestosteronemia) against the background of low gonadotropic hypophysis activity (slide 3 and 4 A.N.). On the stage of 1991-1992 appeared the tendency to increase of basal testosterone secretion that was less in patients after ARS II and III.

Prolactin in reactions of effort and compensation, as a somatotropic hormone too, promotes to increase organism energy, intensifies hyperglycaemic and lipotropic effects and gluconeogenesis, so it is the synergist of cortisol. Protracted increase of prolactin concentration in blood can promote to creation of metabolic background that would cause the development of atherosclerosis. There is some date that points out the connection of this hormone high concentration with atherogenic types of dislipoproteinemia and cerebral atherosclerosis.

Protracted increase of prolactin level in individuals after ARS in combination with other changes of hormonal homeostasis shows the complicated regulative reconstruction of irradiated organism. This evolution requires further studying.

Oscillations of indexes which characterize the thyroid gland function didn't determine till now. In 6 persons were determined the hypofunction not confirmed by the results of hormonal investigations in dynamics.

The post-radiation changes of hormonal function have the protective, adaptive and compensative directions which allow organism to overcome post radiation effects, but from another side in consequence of long term of action it can be the basis of further regulative and metabolic pathology.

Approximately in half patients have been revealed atherogenic changes of lipid metabolism. The frequency and heaviness of disorders didn't depend of received dose. We separated groups of patients with steady and progressive disturbances of lipid metabolism according to dislipoproteinemia types and atherogenic coefficient.

Individuals with essential decrease of cholesterol level during observation were included in special oncogenic risk group.

There were determined the definite changes in different lipid classes (phosphatidilholins, sphingomyelin, cholesterol) and densitometric indexes of polyamine. The polyamine investigation has the definite meaning in diagnosis of oncogenic processes on all stages of radiation defeat development including remote period. it is explains of their role in regulation of cells' responses which realized through the processes of phosphorylase polyamine-depended proteinkinaz reactions, protein synthesis, proliferation and cells growth. In individuals after ARS 5-6 years later Chernobyl accidents have revealed essential increase in blood serum the spermia and putrescine concentration and this fact probably connects with increase of their biosynthesis as the result of ornithine decarboxilaz and spermidinsynthetaz activation.

In erythrocytes of persons after ARS were revealed the changes of activity of enzymes of antioxidant defense, activation the processes of peroxide oxidize of lipids, weakening the mechanism of antiradical defense, increase of membranes affect and activity of lysosomal enzymes.

Hyperenzimemia is the evidence of destructive components on the cells' and tissues' level and is the prognostic negative sign which characterizes the severity of pathological state.

There was determine din patients after ARS in 1991-1992 the essential decrease of hemoluminiscence indexes (indexes of common lightsome) what can characterize the fall of level of peroxide system energetic abilities and can create the definite risk of remote sequence's development.

We received the evidence of common metabolism disorders, changes in mediator's metabolism which were revealed 5-6 years later after accident.

In recent time there were revealed 7 cases of radiation cataract. There was no one case with cancer in persons with real ARS. Among patients with not confirmed ARS was one case of lethal sarcoma of thigh.

Conclusions

1. The steady and increasing hypercortizolemia and increase of ACTH concentration which changed on their sharp decrease;

2. Steady hypotestosteronemia and low level of LH;

3. Steady prolactin level which is the factor of nonspecific adaptation;

4. Increase of polyanime (apermine and putressin) blood concentration as markers of probable tumour;

5. Atherogenic changes of lipid metabolism (in half of patients);

6. Changes in enzymes of erythrocytes show the destructive components of radiation includence on cells and tissues levels;

7. Chronic diseases of different organs, decrease of physical and mental working capacity, effectiveness of energetic supply of physical work, increase the number of patients with disablement;

8. Transformation neurovegetative and psychoneurological disorders in organic neurovascular pathology (arterial hypertension, discirculatory encephalopathy, psychoorganic syndrome with change of personality) 5-8 years later after the accident.

Late radiation effects were studied not only in Ars patients but in other groups of irradiated population. Realisation of estimated irradiation effects was seen only in the group of children with thyroid cancer. Other abnormalities on the tissue and organic level were not foreseen before These changes were characterised by a large number of functional abnormalities which had transformed to a stable pathology especially in ARS patients.
Broncho-pulmonary, gastro-intestinal, cardiovascular and nervous systems pathology were of first-line interest.

In result of analysis of liquidators' pathology including patients after ARS we made the main conclusions about:

Haematopoiesis:

1. It is more frequently found the lysis process in the cells of peripheral blood and bone marrow that is shown in decrease of oxygen-recovery process and increase of lysis process;

2. It is more frequently found stable and non stable chromosomal aberration in liquidators;

3. It is changed the quantity and quality indexes of blood: the decrease of leucopenia from 13% in 1986 till 3% 1993 and the increase of leucocytosis from 4% till 15%, in 1986 there was lymphocytoses and eosinophilic and 1993 monocytosis.

Digestive tract:

Prelevance of erosion and ulcer diseases in digestive pathology, their prolong duration;

Mortality: (Study 178 cases, who died in 1988-1993)

30% - cardiovascular pathology;
19% - suicides;
13% - alcoholic poisoning and trauma in this condition,
8% - oncological pathology.

Main Conclusion

The represented data shows some prelevance of our databases:

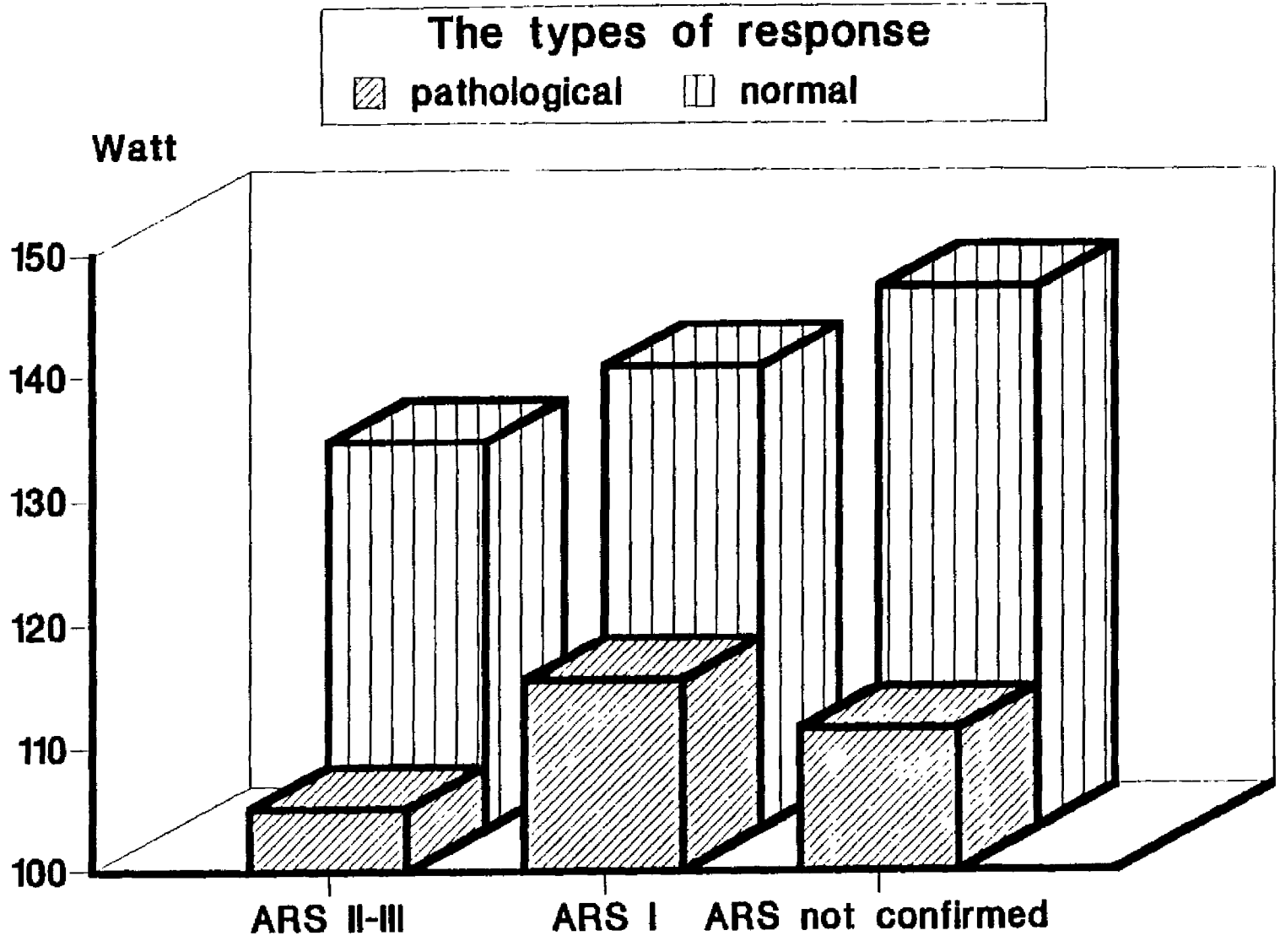
1. They have included all cohorts of victims in results of Chernobyl accident;
2. They allow to determine all risk-groups of stochastic and non stochastic.

But we see some shortcomings (defects):

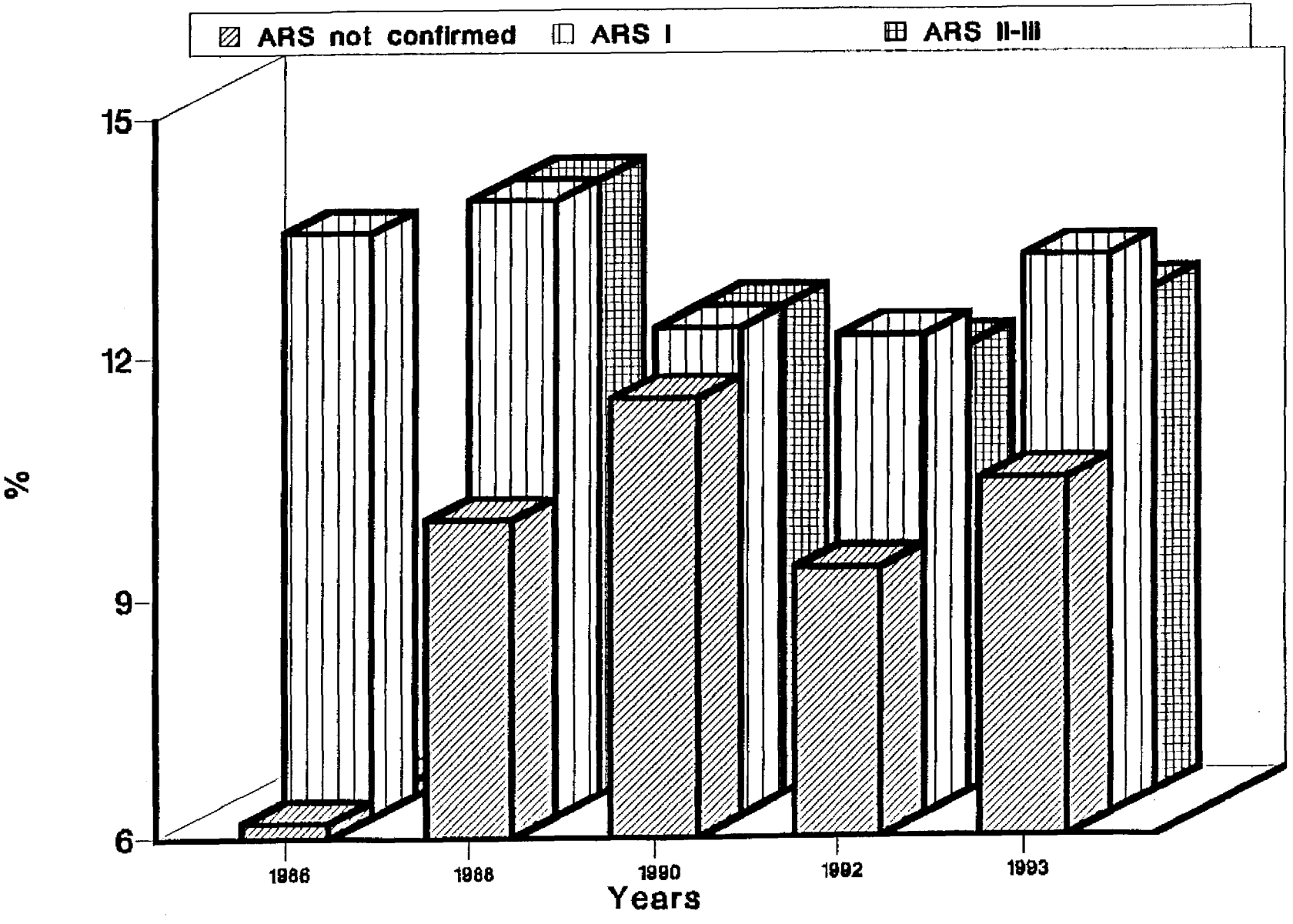
1) They can't provide the systemic approach to investigation of promote consequences because thez not conected with each other So thez not help us to connect the results of investigations on different levels of integration· mollecular and cellular, tissue, organs, arganisms and population;

2) They can't allow to use new methodological approaches in studing of victims.

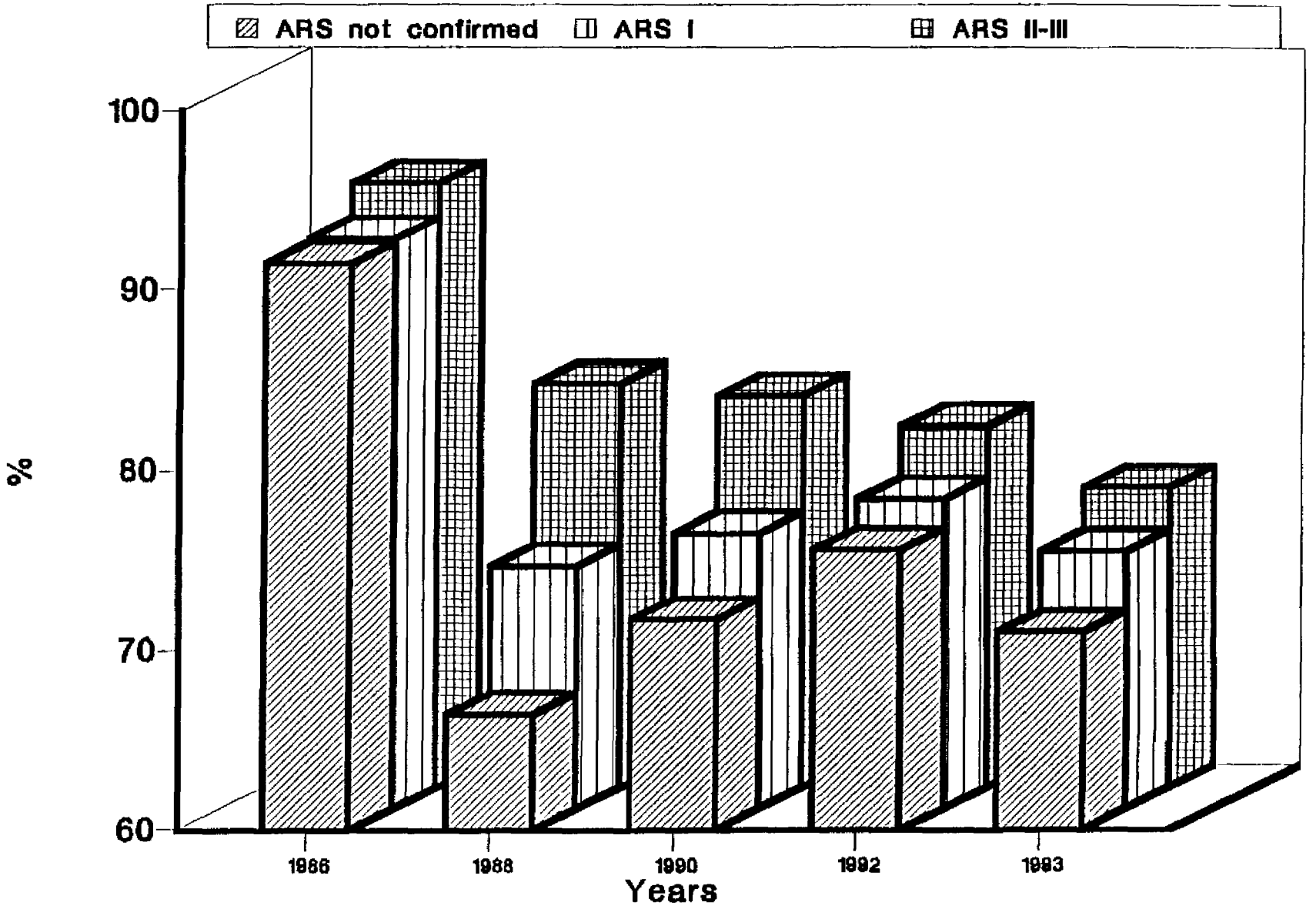
So we must to create the unique database that would include all fields of investigation with different levels. This would be the tool for studying of stochastic and non stochastic effects of irradiation.



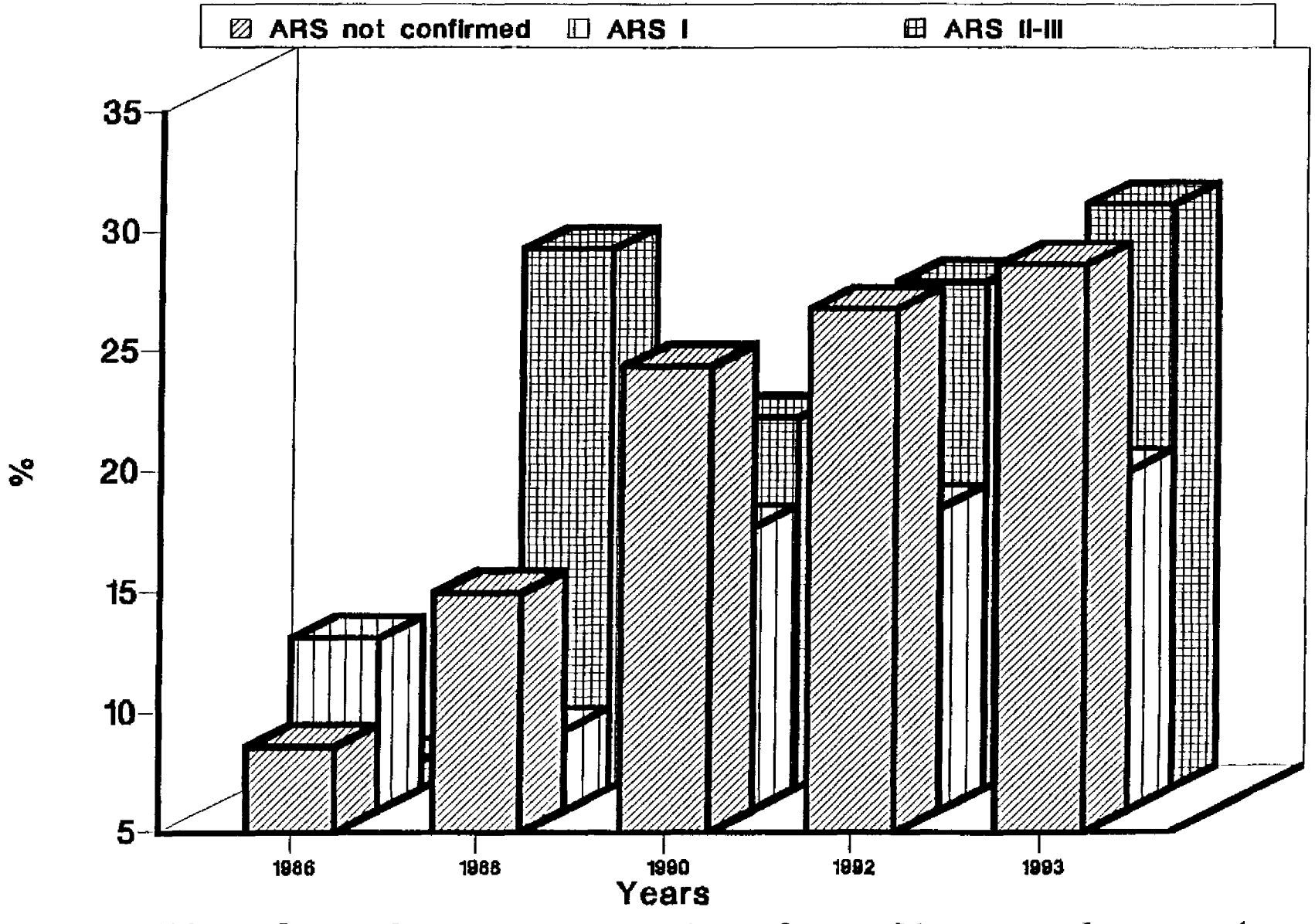
The tolerance level to physical work in patients after ARS with pathological and normal response of circulation



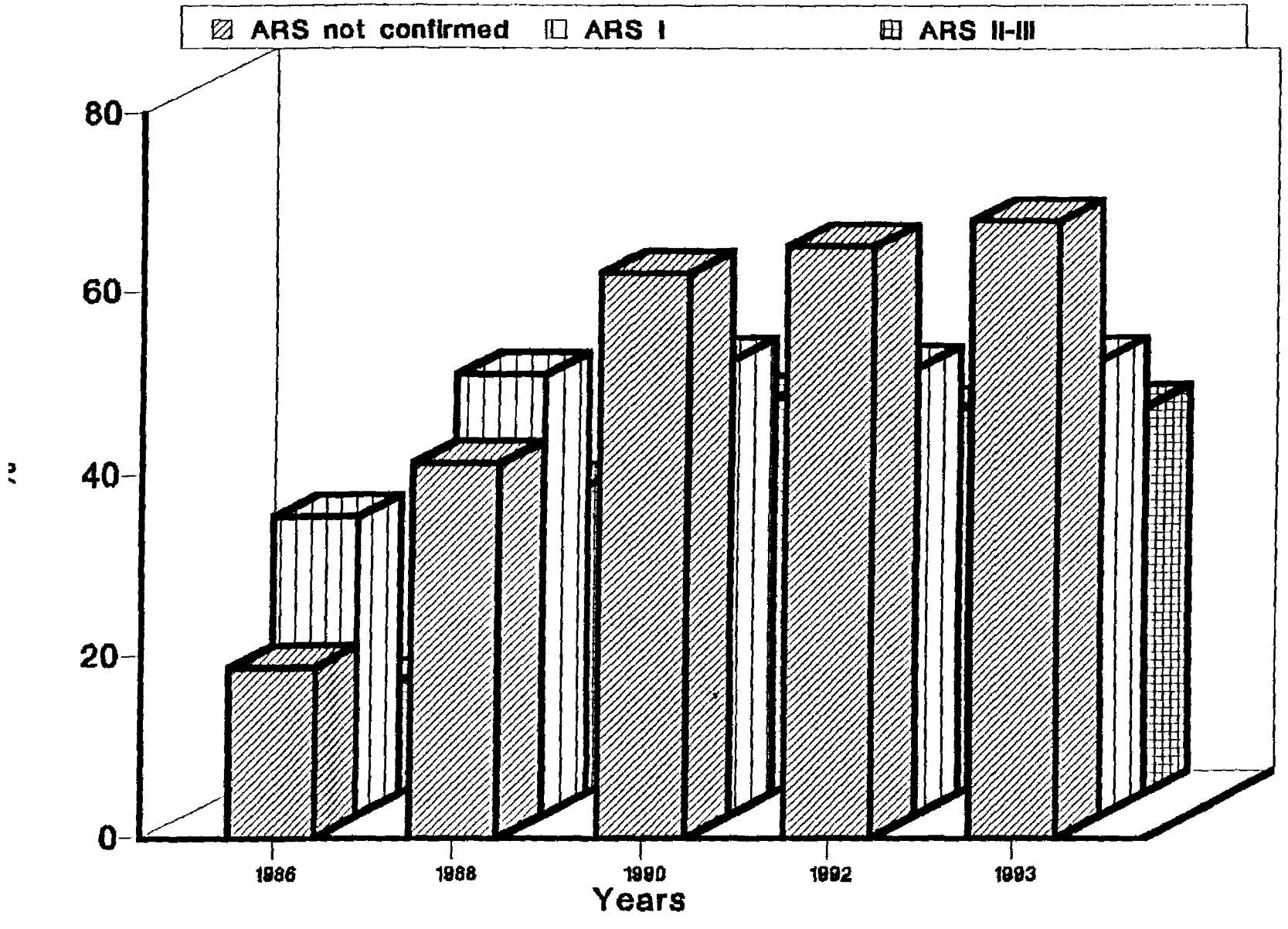
Disorders frequency rate of respiratory system in individuals who have ARS in relation with Chernobyl's accident



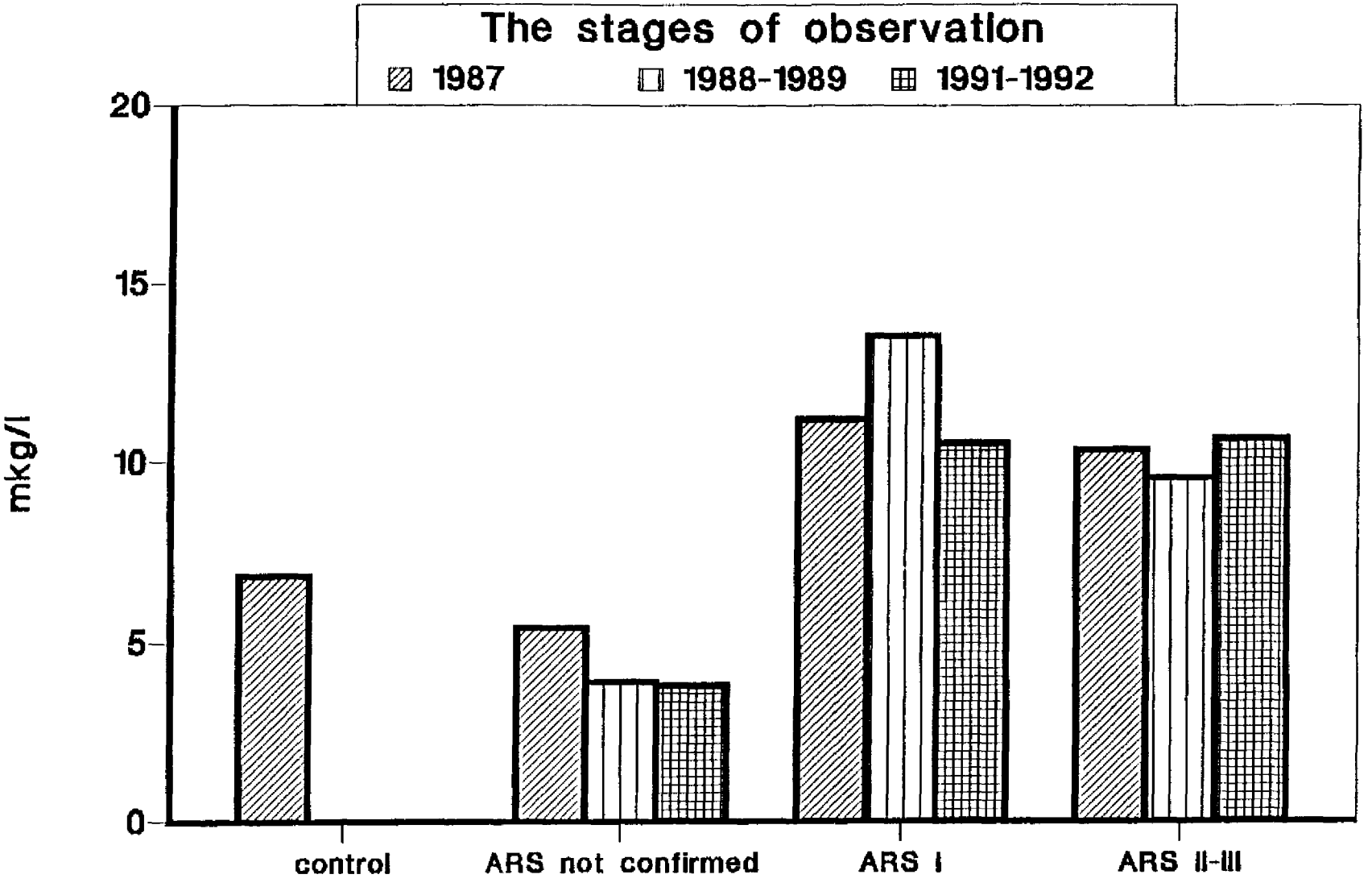
Disorders frequency rate of nervous system in individuals who have ARS in relation with Chernobyl's accident



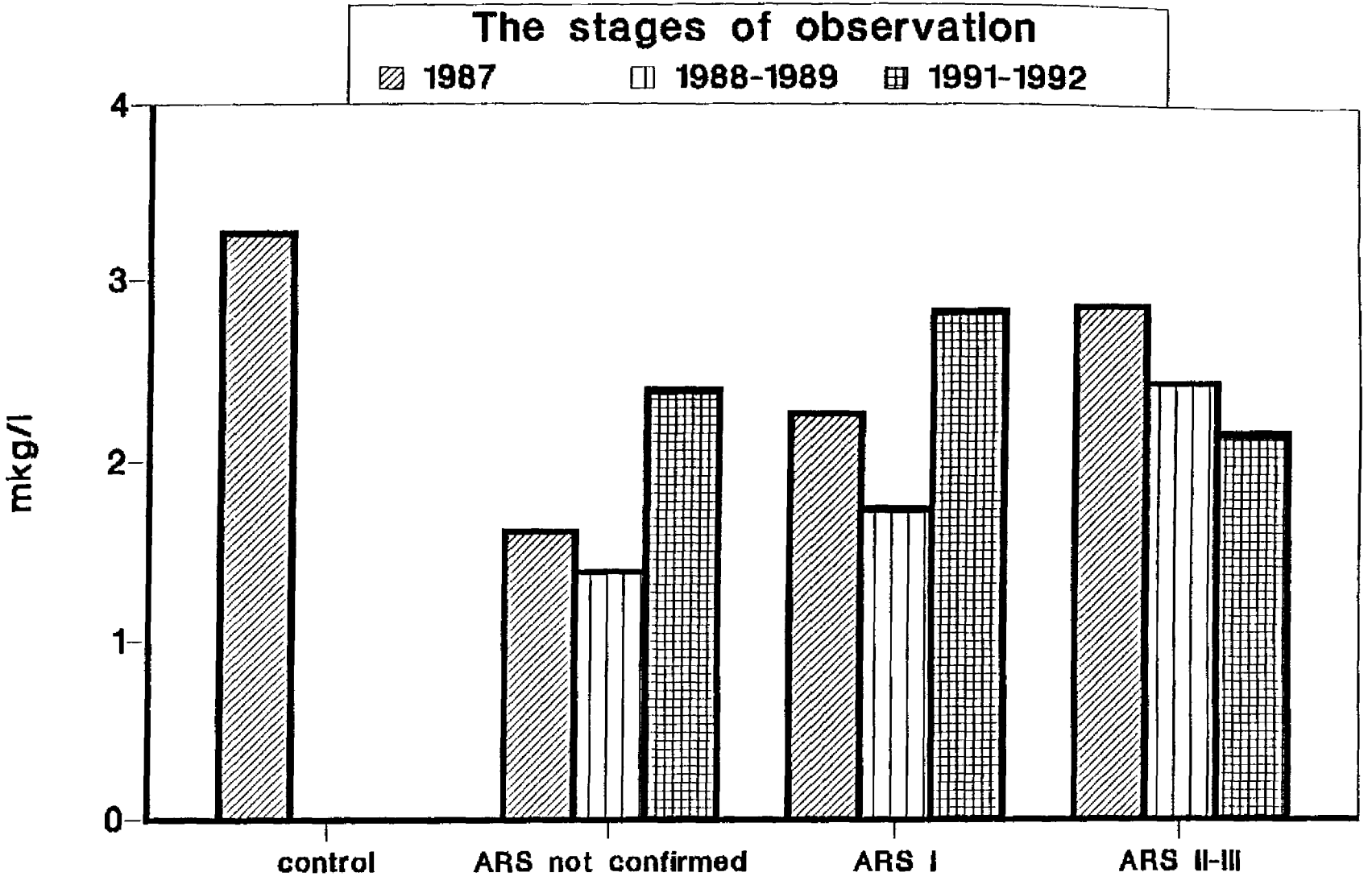
Disorders frequency rate of cardiovascular system in individuals who have ARS in relation with Chernobyl's accident



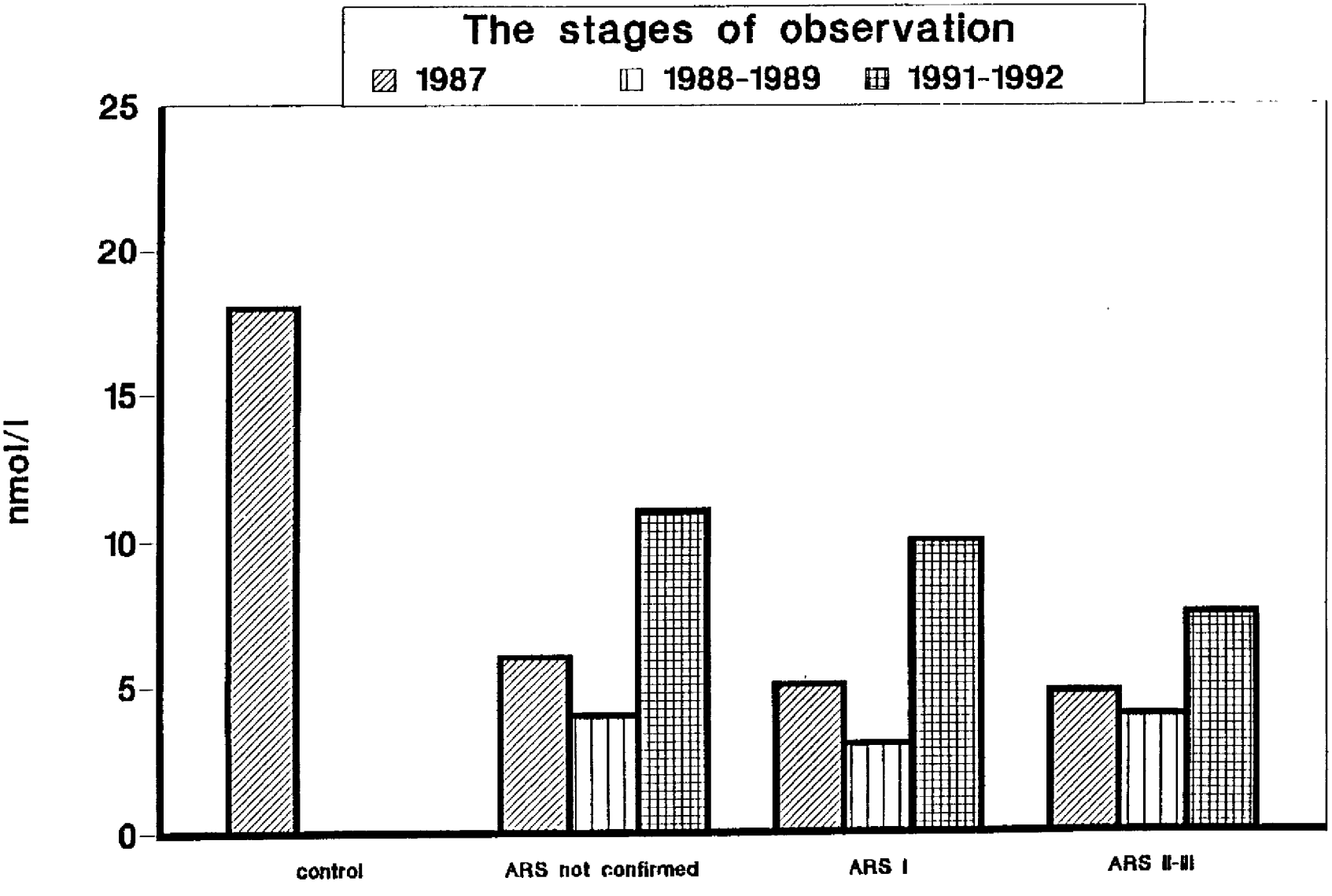
Disorders frequency rate of digestive tract in individuals who have ARS in relation with Chernobyl's accident



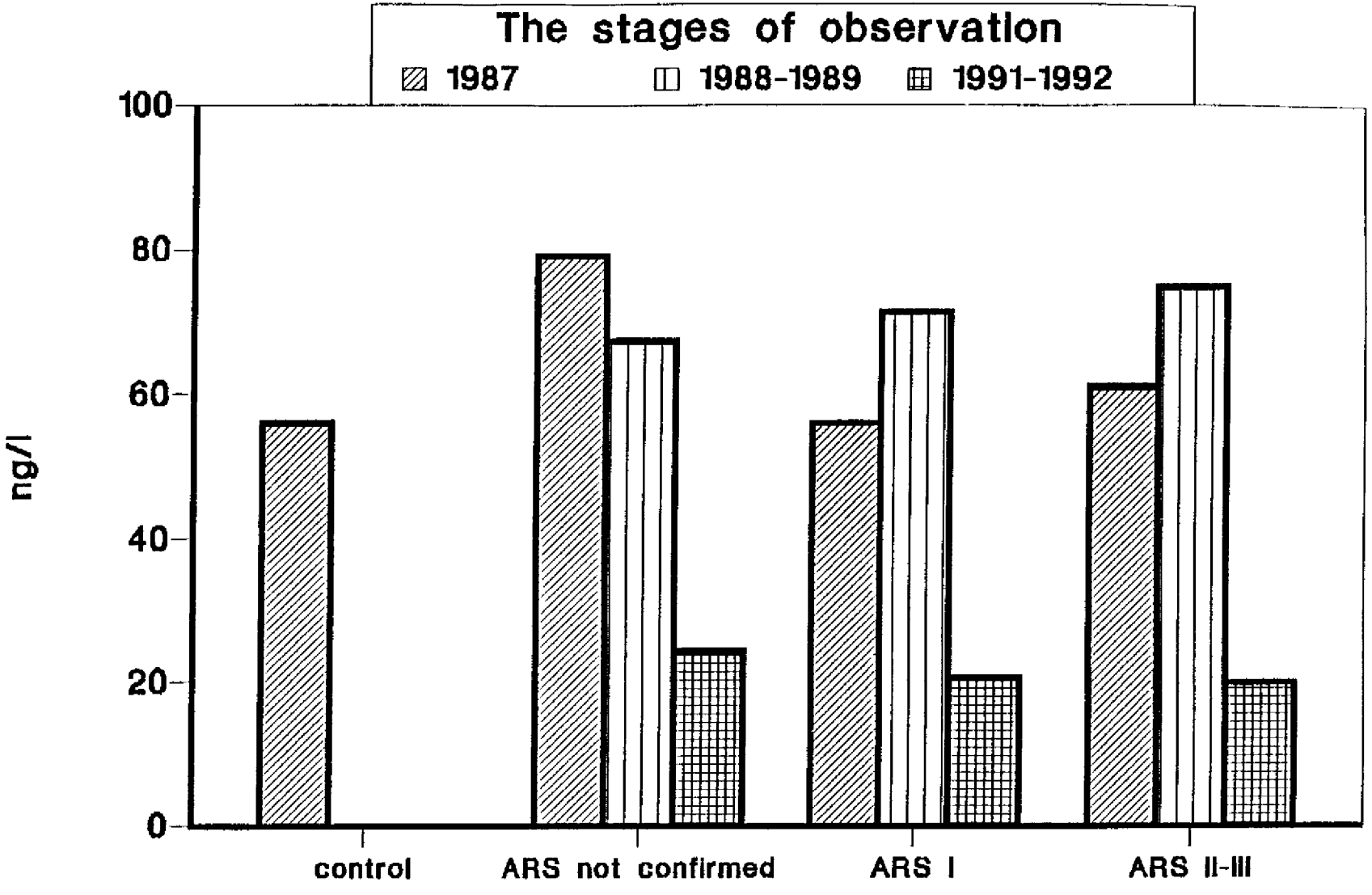
The dynamics of serum prolactin concentration in individuals who have ARS in relation with Chernobyl's accident



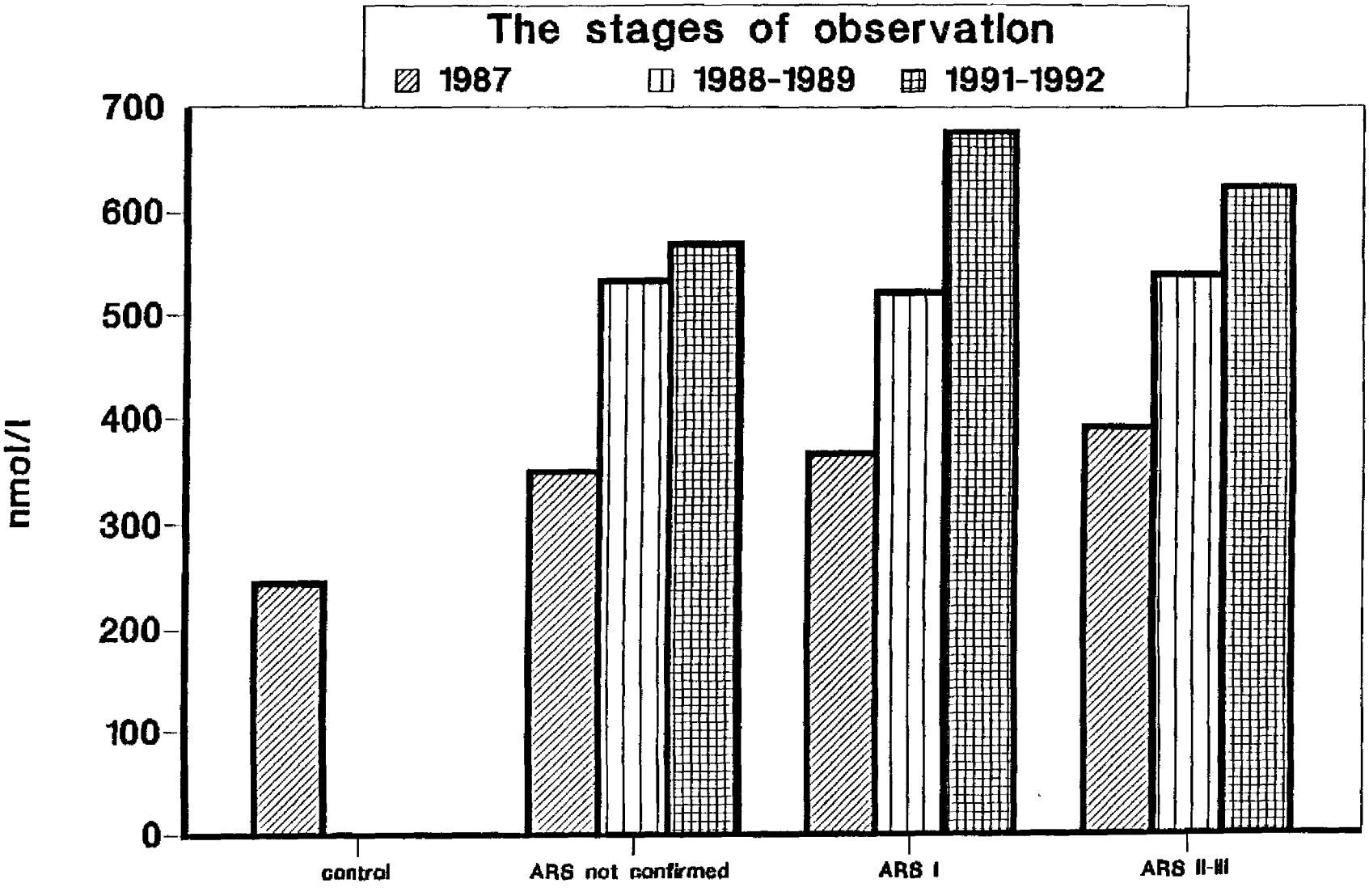
The dynamics of serum LH concentration in individuals who have ARS in relation with Chernobyl's accident



The dynamics of serum testosteron concentration in individuals who have ARS in relation with Chernobyl's accident



The dynamics of plasma ACTH concentration in individuals who have ARS in relation with Chernobyl's accident



The dynamics of serum cortisol concentratio in individuals who have ARS in relation with Chernobyl's accident

The Institute Curie Experience

Presented by Dr J.M. Collet

CLINICAL RADIOPATHOLOGY

THE INSTITUTE CURIE EXPERIENCE

1951 - 1994

I.C. CLINICAL RADIOPATHOLOGY
(1951-1994)

TOTAL NUMBER OF PATIENTS

952

I.C. CLINICAL RADIOPATHOLOGY

- Accidental irradiation	560	59%
- Radiotherapy sequelae and complications	338	35%
- Radiophobia	56	6%

I.C. CLINICAL RADIOPATHOLOGY

- **Accidental irradiations: 560**

I.C. CLINICAL RADIOPATHOLOGY

- Accidental external irradiations : 457

1. Total body irradiations : 136 (30 %)
   - 118 minor hematological and/or clinical symptoms
   - 18 major symptomatology (3 deaths)

I.C. CLINICAL RADIOPATHOLOGY

- Accidental external irradiations : 457

2. Localized irradiations : 256 (56 %)
   - 196 : one site
   - 60 : several sites

I.C. CLINICAL RADIOPATHOLOGY

- Accidental external irradiation : 457

3. Associations : 65 (14 %)
   - Total body + localized irradiation : 54
   - External + internal : 11

I.C. CLINICAL RADIOPATHOLOGY

- Accidental contaminations : 103
   - Aerodigestive tract 41
   - Cutaneous 59
   - Systemic 3

I.C. CLINICAL RADIOPATHOLOGY

Among the 560 accidental irradiations (external + contamination)

148 "suspicious" accidents, which were not confirmed either by

- Physical reconstruction

or - Biological dosimetry

or - both

I.C. CLINICAL RADIOPATHOLOGY

Radiotherapy sequelae / complications : 338

- Treatment of fibrosis (115 SOD)
  - Breast : 255
  - Bone tumors : 31
  - other : 19
- Preventive SOD protocol of rectal fibrosis : 33

I.C. CLINICAL RADIOPATHOLOGY

- 144 treatments
  - symptomatic TT 66
  - surgery alone 13
  - SOD 9
  - combined treatments 56
- 416 untreated

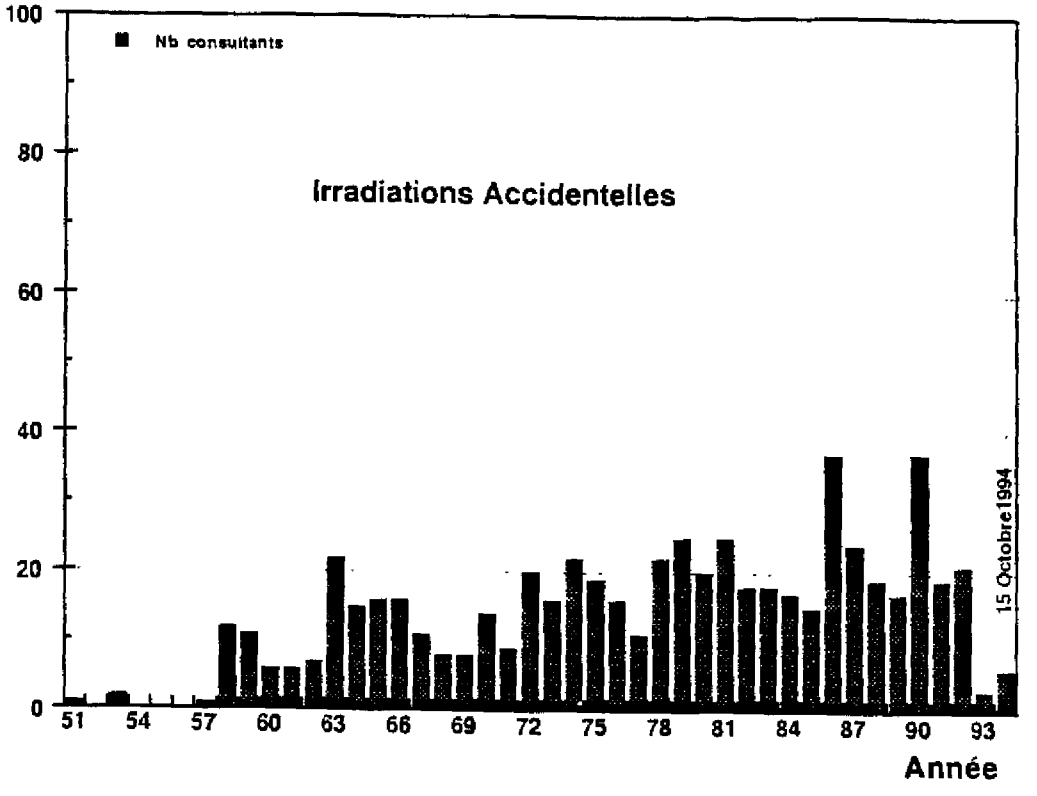
  148 actually non-irradiated

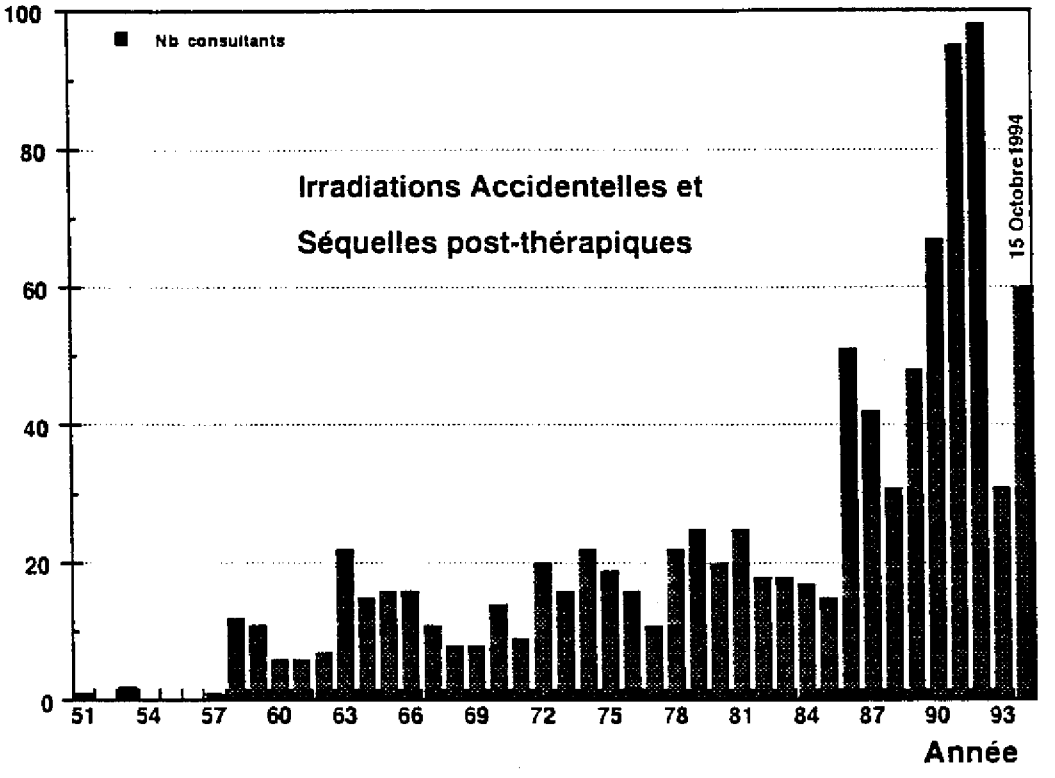
I.C. CLINICAL RADIOPATHOLOGY

- Evolution after treatment
  - 51 cases of major sequelae including amputations
  - 3 deaths (see above)

I.C. CLINICAL RADIOPATHOLOGY

Number of cases as a function of time :




Nb consultants
Irradiations Accidentelles et
Séquelles post-thérapiques
15 Octobre 1994
100
80
60
40
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0
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Année