Chapter 1. HISTORICAL SKETCH: 1896ж1945

1.1. First steps (1896 ж 1906)

Radiobiology as the science started with the studies of X-rays effects on central nervous system. The first in the World scientific work devoted to the *study of ionising radiation impact on the Central Nervous System* was conducted by I.P.Tarkhanov (Tarkhnishvivli, Tarkhan–Mouravy) in 1986 in Biological Laboratory St. Petersburg University a few months after the X-rays phenomenon description was published. I.P.Tarkhanov explored the skin-galvanic (psycho-galvanic) reflex and therefore presented the biophysical direction in physiology himself. In 1896 applying the physiological method I.P.Tarkhanov observed the acid reflexes substantial depression up to the reaction ability on acid solution complete absence. He stated that the X-rays exposure for quarter the hour makes quieting effect on frogs resulting in rough decrease in general locomotive activity. The observed after irradiation reflexes depression he explained not by the X-rays-induced dulling of skin sensitivity but by the depressing effect on the central nervous system. I.P.Tarkhanov managed in experiment to shut down by X-rays the strychnine-induced convulsions arise in frogs that enabled him to substantiate the *hypothesis of ionizing radiation depressing effects on the central nervous system.* Basing on his experiments results I.P. Tarkhanov firstly expressed the idea of X-rays application not only for diagnostics but also for the *treatment* of patients. But the assumption of I.P. Tarkhanov concerning the ionizing radiation anti-convulsive effect was not proved in further.

I.P. Tarkhanov (1896) made the first try to study the neuro-muscular apparatus functional status changes. But he received the negative result exposing with radium beams the interpolar space of nervous fiber or muscle, observing no irritability changes.

The pioneer works of I.P.Tarkhanov significance is first of all in the *physiological research methods choice* but not only the morphological changes studying, not been observed under the at that time ordinary applied X-ray doses.

Just 90 days after the X-rays discovery publication by W.K. Roentgen the first information about complaints on severe visual disorders in fluoroscopic devices operators was received. But it remained not clear whereas that was resulted from visual overstrain or the ionizing radiation impact. Th.Edison who intensively tried to work out the fluorescent lamp suffered the visual disorder that required emergent medical intervention [Miller R.W., 1995].

Th.A. Edison (1896) in his work *«The Blind Man Can See a Bit»* marked the ability to see the arm movement with closed or even tied eyes in case when the hand was placed between radiation source and eye. Such kind visual sensations were described both by the radiation direct effect on retina and eye mediums fluorescence generating.

In 1896 Mr. Aksenfeld for the first time reported that various insects and Crustacea placed in the not exposed to radiation dark side of the wooden box move to the irradiated part soon after the exposure initiation — i.e. *direct behavior reactions on irradiation* were revealed for the first time [Citated after D. Kimeldorph and E. Hunt, 1969].

G. Branges & E. Dorn (1896) were ones of the first who observed the visual light sensations under X-rays exposure of the eyes — *radiophosphenum.* Thus more than a century before the extremely important discovery was made — *ionizing radiation detection possibility by the organs of sense.*

Following the work of I.P. Tarkhanov the study results of Uden, Bartelemy and Daryet (1897) was published. Exposing the Guinea Pigs to X-rays they revealed *neurological symptoms (extremities tremor, tactile sensitivity disorders and paralyses).* But the authors could find no *any anatomic changes* in nervous system. No any histological changes were registered by other researchers in nervous system tissue of rabbits exposed to radiation. Kinbeck (1091) after the exposure to Roentgen beams found *neither functional, nor histological changes in central nervous system.* The drowsiness, convulsions and paralyses followed by *death* of animals arose after the irradiation author connected to the «brain tissue inflammation or toxicosis» [Cited M.I. Nemenov, 1950].

F. Himstedt & W.A. Nagel (1902) were first who studied the *«retinal electric reactions»* under the X-rays impact. They observed deviations of electromotive force between cornea and eye posterior pole under X-rays exposure. Reaction was much more expressed in animals (with layer of rods prevalence in retina) being in adaptation status to the darkness.

M.O. Zhukovsky in 1903 conducted observations in dogs aiming the ionising radiation impact on *cortex irritability* revealing. Irritability elevation occurred after the exposure of the brain locomotive zones to γ-radiation from 10–15 mg of Radium Bromide salt for 12–40 minutes through the trepanation hole in the cranium. Extension of front and back extremities from inductive current impact on respective cortex centers was the index of cortex irritation value. Duration of elevated irritability period was in direct dependence on absorbed irradiation dose. M.O. Zhukovsky fixed that directly after the irradiation the *irritability is elevated* and then becomes *lower than normal.* After the repeated irradiation series the irritability not increased but continued to decrease.

J. Danysz in 1903 injected the Radium salt to the mice subcutaneously in the zones of brain and spinal cord. In young animals age up to 1 month he observed *paralyses and paraparalyses* within 3 hours and *convulsions* — 7–8 hours after. *Death* of animals occurred 12 - 18 hours after the irradiation. In animals with age over 1 year death occurred after 6–10 days under the same doses impact. Besides that J. Danysz observed *paralyses* in mice 44 days after the total body irradiation, as the result of what animals died. In Guinea Pigs Complete paralyses were observed in 8–12 days old Guinea Pigs with Radium salts — containing capillary inserted tied subcutaneously near the vertebral lumbar part, similar to the tetanus poisons effects and animals died 6–8 days after. Adult animals under such procedure revealed no immediate nervous events and died several weeks or months after because of infection. Brain microscopy revealed the cerebral vessels expressed disorders with no changes being present in nervous cells themselves. Thus J. Danysz was the first who noticed the *age aspects of neuroradiology* and pointed out on the *vascular disorders* importance in brain radiation damage pathogenesis.

E.S. London (1903) exposed mice to the total irradiation from 30 mg of Radium Bromide for three days period. All the exposed animals presented *languidness, refuse from food, drowsiness, hypo- and hyperreflexia, back extremities paralyses*. Animals died 5–6 days after the irradiation. Changes in *big hemispheres cortex* were registered histologically. The same events were fixed in rabbits too. Besides that, E.C. London (1904) conducted the experiments in human aiming the big hemispheres irritation induction through the occipital lobe exposure to the Radium preparation placed near the occiput. As the result the *light sensations (phosphenes)* were observed.

Similar results were received by S.V. Goldberg. He induced the *sharp agitation, clonic and tonic convulsions with further paralyses* by means of dog *brain* irradiation (75 mg Radium for 7 hours) through the trepanation hole in the cranium. Nissel substance dispersion and neural cell chromatolysis was observed in brain tissue histological study. He pointed out that X-rays induce the same effect as the radium preparations irradiation. Neural cells chromatolysis author considered the death reason in exposed animals.

German researcher H. Heineke (1903) in lethal doses of total irradiation with Radium of mice and Guinea Pigs revealed the chromaffin substance shift to the cell circumference in *brain* cortex ganglionic cells under staining by Nissel. W. Scholz (1904) under the lethal total irradiation of the mice, rabbits and Guinea Pigs was unable to reveal the histological changes in neural cells of irradiated animals. Only the brain vascular changes were observed. H. Obersteiner (1904) came to the similar conclusions.

At the same time L.M. Gorovitz (1906) came to conclusion of the nervous tissue highest sensitivity to radiation, as the result of morphological study held among the rabbits. In her dissertation work «To the Study of Radium Beams Biological Role», defended in the Army Medical College, St.Petersburg in 1906, she noted: *«...for the sensitivity to the radium impact the tissues and viscera can be selected in three groups: nervous tissue, gonads and lymphoid organs ... are related to the first one...»*.

Consequently, already in 1896–1906 period the nervous system radiosensitivity phenomenon was demonstrated on the background of physiological and morphological experimental study results. Shortcomings of ionising radiation application and dosimetry can be considered as the disadvantage of those pioneer research.

1.2. Comingжtoжbe Period (1906ж1945)

1.2.1. Radiation-induced Structure-Morphological Changes of Nervous System

In 1906 the French physicians J.A. Bergonie & L. Tribondeau established the rule presenting dependence of some properties of living organism cells and their sensitivity to ionising radiation. Further that rule was named *«Bergonie & Tribondeau Law»*. The Law postulates that the radiation causes the more intensive effect on cells if more high is their proliferation activity, more long is their karyokinetic process and less differentiated are their morphology and function. This Law is the cornerstone of radiotherapy practical application that is based upon different radiosensitivity of normal and pathological cells.

Within all the period after Bergonie & Tribondeau Law was formulated it was subjected to critics focused mainly on its localiseness and cell reaction description isolated from organism status in a whole. Nevertheless at present in the world literature it is considered as the basic rule in ionising radiation biological effects study.

Since 1906 series of works were published concerning the conclusions of the mature nervous system high redioresistance made on the basis of only the morphological studies results [Sicardo & Bayer J., 1907; Bajer J., 1911; Horsley & Finzi, 1991; Brunner H., 1920; Bagg A.J., 1921; Edwards D.S. & Bagg A.G., 1923; Davis & Culter, 1933 etc.]. Zeitz & Wintz (1920) placed the nervous system on the pre-last place for radiosensitivity in all the tissue row. Only the bones they considered being more less radiosensitive. Wetterer (1920), Heineke (1928) considered lymphocytes the most radiosensitive cells in organism and nervous ones — the most radioresistant. At the same time statements issued just in 1903 by J. Danysz concerning the higher radiosensitivity of *developing nervous system* remained actual and were further developed. Forsterling (1906) established that pups and young rabbits after both total irradiation and head exposure retarded in growth, they presented spastic paralyses and after they died.

Horsley & Finzi (1911) exposed the monkey *brain* to γ-irradiation from 55–100 mg of Radium Bromide for 2–5 hours. Brain membrane thinning and brain vessels changes were fixed in histological study. Nervous cells were remaining intact. Authors concluded that γ-rays not effect the nervous system but only the cerebral vessels.

R. Balli (1915) observed the fibril netting structure disorders in nervous cells of dogs and Guinea Pigs under the *spinal* cord exposure to Roentgen rays.

H. Brunner (1920) found out the cerebellar outer granular layer absence and focal injuries in the inner granular layer in kitten and pups *brain* one-time X-ray exposure to the four erythemal doses. Those changes were more expressed in pups. But even in case of animals exposure to enormous (7–40 erythemal) doses he revealed only *vascular changes* — hyperemia, hemorrhages and brain swelling. This author also denied the X-rays effects on nervous cells and considered all the phenomenon occurring as the result of vascular changes.

H.J. Bagg (1921) applying the Radium emanation in glass ampoule with 127 $mCi \cdot h^{-1}$ activity, inserted directly into the *brain* of rats and dogs revealed brain tissue necrotic changes only close to the implanted ampoule. In other experiments with Radium emanation application with 1,965–12,030 $mCi \cdot h^{-1}$ activity for monkey and dog brain irradiation from outside with 10 mm distance from temporal bone any histological changes of the brain were not revealed.

First the *demyelination* phenomenon under radium preparations impact on *peripheral nerve* was revealed by E.S. Redfield, A.C. Redfield, D. Forbs (1922).

Pendergass et al. (1922) applied low (one should take into account the «low» dosed at that time considered up to 1,000 R [M.I.Nemenov]), high and extremely high radium doses injected with needles into the dog *brain* substance. Brain tissue necrosis and sharp changes of vascular wall etc. were received in high doses. But general systemic symptoms observed in dogs, the authors attributed to toxin allegedly produced in exposed tissue and the death of animals occurring within 2–7 weeks, they regarded the *toxemia*.

K.L. Khilov (1924) for the first time conducted research inducing the *vestibular analyzer* damage under radium emanation impact [Cited Lebedinsky A.V. and Nakhilnitskaya Z.N., 1960].

A.V. Rahmanov (1925), A. Rahmanov (1926) revealed changes only in the *brain* vessels and mesoderm under exposure of X-rays 3 erythemal doses, whereas no any changes in nervous tissue were revealed.

R. Demel (1926) studied the ionizing radiation effects on *developing brain*. Thalamus hemiatrophy with basal ganglions safety, big hemispheres cells degenerative changes, reduction of brain columns with pyramid and rope-like bodies of medulla were observed in 4-days pup under right cranium part exposure to X-rays 2.6 erythemal doses.

B.N. Mogilnitzky and D.Ya. Podljaschuk (1929), B.N. Mogilnitzky and D.Ya.Podljaschuk (1929, 1930) came to conclusion concerning the *developing nervous tissue* higher radiosensitivity compared to the mature one. After X-ray irradiation of pup and rabbit whelps heads in very high doses (2 to 10 erythemal doses) they revealed cytoarchitecture disorders and ganglionic cells changes, whereas in adult animals only the connective tissue elements reaction, neuroglia and epindima proliferation, spinal cord channel dilatation after irradiation, but found no changes of nervous cells. B.N. Mogilnitzky and D.Ya. Podljaschuk (1930) studied the rabbit head X-ray exposure effect on *haemato-encephalic barrier permeability* for trypan blue. No permeability changes were registered after exposure to 3.5–10.5 erythemal doses. Permeability increased after 3–5 irradiation sessions with 4–6 erythemal doses.

M.S. Lutershtein and A.V. Ranmanov (1929) studied the ionising radiation impact on skin *sensitive nervous ends*. Epilation and skin substantial erosions were observed in mice after X-ray irradiation of back caudal body part. Epidermis thikened in 5–7 times due to layers number increase. Nervous fibers grew through in the epidermis forming long and ramified filaments. Merkel cells partially degenerated, partially were present in epidermis more superficial layers. Authors marked the nervous fibers intensive growth being pathological phenomenon and they considered ionising radiation initially effecting nervous fibers.

M.N. Meissel (1930) revealed *subepitelial, intraepitelial and connecting tissue nerves* excessive growth in white mice after 1,000 – 3,000 X-rays irradiation on the back. All the tissues necrosis including the nervous one was observed after irradiation in high doses due to ampoules with radon implanting subcutaneously. Nervous fibers atypical branching was observed in newly regenerating epithelium.

D.G. Shefer (1933, 1934, 1936) revealed hyperemia, brain tissue swelling and small extravasations in 2–4 month-old pups irradiated on *temporal zones* with 1.5–5 erythemal doses of X-rays. Degenerative changes in *cortex cells and diencephalon subcortex ganglions* and less expressed ones in brainstem and cerebellum were found in pups after exposure to 4–5 erythemal doses. The same but less expressed changes were also present after 1.5–2.0 erythemal doses application. After head exposure to X-rays 4–5 erythemal doses the degenerative changes in vessel walls, slight brain swelling and astrocytes degeneration were revealed in dogs. No changes were revealed in nervous tissue. Sharp vascular disorders and blurred degenerative processes in *lateral and posterior horns cells* and around the central channel were marked after similar radiation exposure of *spinal cord* in dogs. D.G. Shefer concluded that ionising radiation initially effects the nervous cells in young animals that was confirmed by presence of both sharply changed and undamaged cells within range of vision, that hardly can be explained by the blood circulation disorders.

R.S. Lyman, P.S. Kupalow, W. Scholz (1933) explored X-ray high doses impact on *brain* in adult dogs. The head occipital zone was exposed to 18–20 erythemal doses. Pia mater inflammation and plasmatic transudation around small vessels were observed 5 – 6 weeks later. Histological study revealed both vascular changes and nervous cells damage especially in dog that remained alive for 6 months. The mentioned study was conducted by W. Scholz, neurohistologist from Munich that was resolute follower of idea of neural cells damage absence under the X-ray exposure. That is why the vascular disorders were considered the necrosis reason. But P.S. Kupalow turning back to this issue in 1959 pointed out to the nervous cells initial structural changes possibility after irradiation that could be not registered by routine histological techniques. Higher nervous function disorders in irradiated dogs served the evidence for this statement with nervous cells functional changes considered by author as the background.

Davis & Culter (1933) revealed changes in the exposed zone with small vessels dilatation and thrombosis by means of *brain* histological study in cats, dogs and monkey after 1–4 mg of radium injection (equivalent to (3.7–14.8) $\cdot 10^7$ Bq) under the dura mater. Only mild changes were found in the nervous cells.

B.J. Alpers & H.K. Pancoast (1933) in brain histological study after roentgentherapy on 3 fields of human *brain* with 600 R in 2–3 times with 2–3 months interval, revealed cortex cells fatty alterations not considered the irradiation consequences. But under *fossa cranii posterior* irradiation with doses reaching 18,000 R (fractionally) they revealed pathological changes in Purkinje's cells and their number decrease.

H. Griffith & E. Pendergass (1934) revealed no degeneration process in peripheral nervous plexuses structure after X-ray irradiation with 80 R of *pre-vertebral ganglions* in rats.

W. Scholz (1934) observed the brain membranes vessels injection after radium beams lethal irradiation of young rabbits head. But no *brain* macroscopic changes were revealed there. In his another work W. Scholz (1935) revealed necrosis focuses in *developing brain* in 9–40 days-old pups after X-ray exposure with 1–2 erythemal doses. But in similarly exposed pups with age 27–50 days no changes of nervous system were found. Author observed the inflammatory processes without brain tissue changes in cases of dissection conduction within 16 hours — 14 days after the exposure. He revealed brain necrotic focuses considering them vascular disorders result 3–12 months after the irradiation with doses not less than 8 erythemal ones. He considered cortex and subcortex ganglionic cells the radioresistant ones in adult animals. G.N. Kassil, S.I. Petrov and M.A. Grushetskaya (1935) fixed in experiments among rats, rabbits and dogs that animal head single exposures to X-rays lead to haemato-encephalic barrier permeability disorders and the recurrent irradiation on the contrary reduces the permeability. Series of works [Natanzon & Nikitin, 1935; D.M.Goldshtein and M.M.Mireskaya, 1937] are devoted to the haemato-encephalic barrier permeability alterations after irradiation but the contradictory results are presented there.

T. Markievich (1935) observed the necrotic focuses in *brain* tissue considering them vascular changes secondary results after X-ray high therapeutic dose irradiation of human cranium part.

D.G. Sheffer (1936) observed degenerative alterations in vascular walls and astrocytes, brain slight swelling both with atrophy degenerative processes in *diencephalon vegetative nuclei cells* after two-sided irradiation of *temporal lobes* in adult dogs with effect threshold of 4 erythemal doses. But in cortex, subcirtex nuclei and brainstem ganglionic cells no particular alterations were revealed. D.G. Sheffer particularly accentuated that *ganglionic cells of vegetative centers are the nervous system most radiosensitive elements*. D.G. Sheffer (1936) also demonstrated that X-rat irradiation of dog head with 0.9–1.5 erythemal doses leads to the *spinal liquor* production decrease and that with 4–5 erythemal doses — provides the spinal liquor production elevation in first days with further sharp drop.

B.N. Mogilnitsky, L.D. Podlyaschuk and M.I. Santotssky (1936) defined that peripheral nerves minor demyelination segments can be revealed in rabbit under X-ray exposure doses of 1,350–1,380 R on extremities and under higher doses — destructive alterations in axis cylinders and myelin fibers.

A.A. Zavarzyn, G.V. Yasvoin, V.Ya. Alaxandrov and G.S. Strelyn (1936) conducted first *radioembriological* studies over the eggs from Leggorn breed hens exposed to X-rays with 0.25–1.5 erythemal doses 12–48 hours after hatching. Under irradiation threshold dose of 0.5 erythemal authors conducted the embryos central nervous system changes histological study and found the nervous cells disintegration with complete absence of apparent embryo blood circulation disorders. At that authors observed that disintegrated by radiation nervous tube can be restored back to the extent of chicken development continuation up to hatching from the egg. In that work on the one hand the embryonic nervous system high radiosensitivity was demonstrated and on the other — the significant potential for regeneration of nervous system in embryo period.

J. O'Connel & A. Brunschwig (1937) revealed degenerative alterations in *brain parenchyma* and considered them primary ones after the X-ray therapeutic irradiation of human cranium with doses 13,275 and 15,400 R (fractionally). Authors came to the conclusion that ionising radiation directly effects the nervous tissue as the degenerated and undamaged nervous cells were present in directly close to each other. At that those radiation alterations involve not only the nervous cells but also the neuroglia and blood vessels with brain parenchyma alterations not being secondary to the vascular disorders.

V. Rascanu, D. Dorogan, M. Kapri (1938) found *myelin* structure alterations after *nerve* irradiation.

B. Baily & A. Brunschwig (1938) revealed necrotic focuses in *big hemispheres cortex* and *cerebellum* that authors considered the radiation direct effect on nervous cells after X-ray impact on head in human with doses 14,000–18,000 (fractionally).

L.M. Davidoff, C.G. Dyke, C.A. Elsberg, T.M. Tarlow (1938) in study of ionising radiation effects on *locomotive functions* determined that resulting events from *brain* and *spinal cord* irradiation in monkeys depend on the applied dose value. Histologic studies revealed alteration sin nervous system.

W. Scholdz & J.K. Hsu (1938) revealed *brain parenchyma* alterations attributed to the blood circulation disorders in histological study of consequences of roentgentherapy with 4 fractional erythemal doses on human cranium section.

R. Abderhalden (1940) conducted the first radioneuroimmunological studies: tissue radiosensitivity evaluation through the definition of threshold dose values arousing the specific tissue proteases emergence in blood. He revealed the *brain cells specific proteases* emergence in blood after application of 247.5 R X-rays on rabbit brain. I.M. Zhdanov (1941) studied histological alterations in rabbit *heart nervous elements and neck sympathetic nodes* after heart zone exposure to roentgen rays with 300–3,000 R dose. The threefold irradiation with doses of 300 R and twofold — with 750 R daily resulted in no alterations in heart nervous elements, neck sympathetic and parasympathetic ganglions. After the twofold irradiation with dose of 1,500 R here and there the nervous fibers swellings in heart were observed.

Ya.E. Shapiro (1941) after alternate bitemporal irradiation of dogs with X-rays integral doses exceeding 2,700 R delivered in 4–6 portions for 10–16 days, revealed in dissection *severe diffuse degenerative process* most of all expressed in *diencephalon*.

F. Ellinger & Ch. Dakison (1942) observed the nervous tissue disorders in fish under X-rays 1,500–10,000 R doses of total irradiation considering them primary ones with effect threshold of 1,500 R. Conclusion of the radiation direct impact in *brain* tissue was enunciated on the basis of vascular alterations similarity both in doses of 1,500 and 10,000 R with the brain tissue disorders increase with the dose elevation.

A. Janzen & S. Warren (1942) under the exposure of *nervus ischiadicum* to the doses exceeding 75,000 R of X-rays in rat revealed nerve and afferent neuron degeneration.

P.S. Henshow (1944) observed in *brain* histological study the Nissel substance dissemination and nuclei swelling in ganglionic cells after X-ray irradiation of mice, guinea pigs and rabbits with doses 50,000 R. But even under the named lethal doses impact resulting in lymphoid tissue complete lysis, no nervous cells disintegration was observed.

L.D. Stevenson & R.E. Ekhard (1945) described the *spinal cord* cervical part myelomalacia after roentgentherapy with 9,800 R integral dose in human for pharynx cancer metastases.

D. Marburg, Ph.R. Resec, R.M. Fleming (1945) found in histological study only the vascular changes and neuroglia atrophy after X-ray and γ-radiation application in fractional doses up to 8,000 R on human *brain* with the cranium bone been destroyed at that by cancer. No alterations of nervous tissue were revealed.

T.I. Wachovsky & H. Chenault (1945) revealed degenerative processes in *brain* tissue not related to the main disease after roentgen irradiation with doses of 13,000–17,000 R fractionally on the human cranium part.

Thereby the scientific data from XX century first part concerning central and peripheral nervous system morphological radiosensitivity were rather contradictory. Point of view about *the nervous system radioresistance* acquired the prevailing position. Even under the extremely high doses impact the nervous system alterations were regarded as secondary ones as the result of vascular disorders.

1.2.2. Clinical Radiocerebral Effects

Clinical neuropsychiatric observations of human irradiation consequences in the XX century beginning mainly were limited to the roentgentherapy cases. Immediately after the Roentgen rays were first applied with therapeutic purpose the ionising radiation general effect on organism became known. Proteins, carbohydrates, salt and cholesterol metabolism alterations arise, blood coagulability and arterial pressure changes occur after the irradiation. The general early reaction onset after the irradiation was registered being called by German authors *«Rontgenkater» — «Roentgen hang-over»*.

But the main disease presence (as a rule — the highly severe one), as the reason for radiotherapy conduction extremely hindered the irradiation effects study themselves. That is why we considered rational to present some results of clinical neuropsychiatric observations over the exposed animals held among the world from 1906 to 1945. One ought to note that any effects extrapolation from animals to human certainly face some limitations especially concerning the higher nervous function.

Forsterling (1906) fixed that pup and young rabbits both after general irradiation and head exposure presented *growth retardation* and *spastic paralyses* with death occurring soon.

Horsley & Finzi (1911) exposed the monkey brain to γ-radiation from 55–100 mg of radium bromide for 2–5 hours. In spite of such intensive radiation impact the authors stated that they revealed *no any functional changes of central nervous system* within 26–45 days since exposure.

R. Balli (1915) observed *pareses* in dogs and guinea pigs after spinal cord X-ray irradiation.

H. Brunner & G. Schwarz (1918) observed *growth retardation, neck muscles trembling, epileptiform attacks and death* 4-days-old pups after low-dose head irradiation to hard roentgen irradiation.

H. Brunner (1920) revealed *cachexia and convulsions* in pups and kittens after the unitary exposure of brain to the X-ray four erythemal doses. *Convulsions and death* occurred in animals after exposure to the huge doses (7 – 40 erythemal ones).

H.J. Bagg (1921) revealed *no any clinical symptoms* after glass ampoule with radium emanation (127 $mCi \cdot h^{-1}$ activity) direct insertion into the dog and rat brain tissue. Within another experiments with radium emanation application (1,965–12,030 $mCi \cdot h^{-1}$ activity) for monkey and dog brain external irradiation with 10 mm distance from temporal zone he observed *salivation and inactivity*.

N.A. Panov (1925) [cited S.B. Danijarov, 1971] describing the *«Roentgen hang-over»* symptomatology after irradiation as *dizziness, nausea, vomiting etc.*, considered that being the result of nervus vagus irritation.

In 20–40th from the pregnant women irradiation for myoma or cancer uteri experience they revealed that *prenatal irradiation* leads to *severe mental disorders*. The extremely severe forms of *central nervous system radiation damage* were described in children irradiated in prenatal period: *microencephaly, microphthalmia, hydrocephaly and psychics defects* [Robinson M.R., 1927; Shall L., 1933; Stocckel W., 1933; Mole R.H., 1986; Davydov B.I., Ushakov I.B., 1987].

Carins & Fulton (1930) observed *muscle weakness of hind extremities and paraparalysis* after spinal cord irradiation in cats and monkeys depending on the doses applied. Monkeys occurred being rather more resistant to radon impact than cats.

S.A. Nikitin and E.P. Maksymchuk (1933) under the *experimental radiation sickness* induced by 2,000–2,700 R doses of X-ray exposure in rabbit described the *«roentgen shock»* occurred 10–15 after the exposure and characterised by the *rapidly increasing agitation changing into depression, convulsive attacks with bawl, urination and defecation resulting in death* within 45–90 minutes after exposure.

Davis & Culter (1933) observed *no any behavior changes* in cats, dogs and monkey after the 1–4 mg radium injection under the dura mater.

G.N. Evergetova, S.I. Zyndberg and R.V. Goryainova (1933) studied the X-rays effects on some psychic functions in child after the scalp exposure for fungal diseases. *Memory and attention weakening* were revealed by means of several psychological tests in 100 children subjected to radiotherapy compared to 500 healthy kids.

R.S. Lyman, P.S. Kupalov, W. Scholz (1933) observed the *higher nervous function expressed disorders* in dogs after head X-ray exposure with 18–20 erythemal doses and in one dog that survived for more long time — *brain severe* *diffuse damage symptoms (ataxia, vision disorders, muscular weakness etc.).* Authors regarded those clinical symptoms to the brain circulation disorders.

W. Scholz (1934) observed the *paralyses* in young rabbit after head lethal irradiation with radium beams. W. Scholz (1953) revealed *growth retardation, epileptic attacks and paralyses* in pups age from 9 to 40 days fter X-ray irradiation with 1–2 erythemagel doses. But in similarly irradiated pups age from 27 to 50 days he revealed only *cachexia* in early period. W. Scholz (1934, 1935) under roentgen rays exposure with 4–20 erythemal doses on mature brain in dogs revealed *no clinical changes* within 9 weeks period after. *Locomotion disorders* were revealed 3–12 months after the irradiation with doses not less than 8 erythemal ones.

T. Markievich (1935) observed *epilepsy, amaurosis and paraparalysis of lower extremities* in human after cranium zone X-ray exposure in high therapeutic doses.

E.I. Bakin, A.N. Naumenko (1938) observed *hyperreflexia, convulsions and than — hind legs paralyses* in frogs after spinal cord exposure to radon.

L.M. Davidoff, C.G. Dyke, C.A. Elsberg, T.M. Tarlow (1938) revealed the «dose—effect» dependence in locomotive functions study in monkey after brain and spinal cord irradiation. Brain exposure to 2,000 R resulted in no any direct changes in animals but two years later involved *the progressing weakness*. Exposure to the doses of 2,000–3,000 R resulted several months later in *hemiparesis*. Under doses exceeding 4,000 R the extremities *paralyses* occurred in the opposite body side to the exposed brain hemisphere. *Ataxia* was observed after cerebellum irradiation with doses over 4,000 R. *Hemiplegia* aroused five months after the spinal cord irradiation with doses of 4,000–5,000.

M.I. Nemenov and co-authors conducted the works for elucidation of moderate radiation doses impact on dog higher nervous function. Dose values involved were usually applied in clinic for cranium fungal diseases therapy in human. M.I. Nemenov and V.V. Yakovleva (1942) noted the conditioned reflex function activation within first 10–15 days after irradiation with 500 R in turn of right and left hemisphere with 24 hour interval. In further the conditioned reflex intensity decreased and remained low for several months. Brain cortex functional loading elevation led to the further depression of conditioned reflexes and paradox reactions genesis. In case of conditioned reflexes combination complication in dogs the higher nervous function disruption occurred with *neurotic condition* genesis.

Thereby in the first part of XX century the clinical observations in the field of radiation neuropsychiatry were owerflown with contradictions. Though of high and very high radiation doses application *some* authors denied in a whole any clinical manifestations of the nervous system disorders, *another* ones described the «neurotic» states arising after the irradiation and the *last* ones denoted the disorders causally associated with ionising radiation impact («roentgen-shock», «roentgen hang-over») down to the radiation organic damage of central nervous system.

1.2.3. Radiation-induced Neuro- and Psychophysiological Effects

First data concerning *peripheral nerve* functional properties disorders under the ionising radiation impact were received by W. Lazarus—Barlow (1913). It was demonstrated then that nerve irritability decrease occurred after radium emanation impact on frog nerve [Cited Lebedinsky A.V., Nakhilnitskaya Z.N., 1960]. E.S.Redfield, A.C.Redfield, D.Forbs (1922) revealed the nerve irritability elevation under the radium emanation low activities impact.

Donato (1926) reported the *vestibular analyser* irratability elevation in men after the medium ear local irradiation with therapeutic purpose [Cited Grigorjev U.G., 1963].

Nevertheless on the background of several histological and some psychological studies results at that time the opinion was formed in scientific literature about mature nervous system extremely high radioresistance. For example H.J. Bagg (1921) under the radium emanation application with 12,030 $mCi{\cdot}h^{-1}$ activity for dog and monkey brain irradiation from outside 10 mm on temporal zone registered no any changes in zoopsychological tests results.

The *neurism* idea turned out being the alternative concept underling works by I.P. Pavlov. Starting since 1927 M.I. Nemenov studied the conditioned reflex function in dogs after head local irradiation. Studies by M.I. Nemenov made real overturn in the field of ionising radiation impact on nervous system studies. His first works were accomplished under personal supervision of I.P. Pavlov. The X-ray exposure of dog head impact on and the *conditioned reflex function* was studied there.

M.I. Nemenov (1932) after the X-rays irradiation with 3,500 R of and 2,800 R 41 days later of dog head observed the *positive conditioned reflexes depression.* After the similar exposure but first to 1,500 R and then 7 days later — to 2,200 R the *positive induction decrease* was registered in the first case and *conditioned reflexes depression* in the second one.

R.S. Lyman, P.S. Kupalov, W. Scholz (1933) observed severe *disorders of higher nervous function* in dogs after head exposure to X-rays with 18–20 erythemal doses. Though only the occipital region was irradiated in dogs the conditioned reflexes function disorders were diffuse and the conditioned reflexes from eye were disordered not more than those from other analysers. All brain cortex parts and even autonomous nervous system centers disorders were observed. Tendency for the conditioned reflexes decrease was observed within first 3 weeks after irradiation being most expressed in dog of weak type. Thereby as early as in 1933 the *higher nervous function type role* was marked *in the nervous system reaction on irradiation*. In the second phase lasting for 12 weeks after irradiation both conditioned and unconditioned reflexes were depressed in dogs.

E. Girden & E. Culler (1933) conducted the experiments series applying Pavlov's conditioned reflexes methodology for *acoustic sensitivity* improvement under the X-ray «moderate doses» impact. Transient threshold decrease to 5.5. dB was observed already after irradiation with integral dose of 39 R. In further Brogden W.J. & Culler E. (1937) revealed the acoustic sensitivity elevation after the unitary exposure to X-rays within dose range 75–675 R. Authors assumed the acoustic effect being the result of cochlea lymph density and viscosity decrease that could reduce mechanic inertia of oscillations transmission processes. They linked those changes in perylymph and endolymph with serum glucose content decrease accounting that to pituitary irradiation [Cited D. Kimeldorf & E. Hunt, 1969].

J. Audiant, D. Auger, F. Fessard (1934) noticed the frog peripheral nerve *irritability* decrease being sometimes reversible after its irradiation with X-rays in extremely high doses (200,000–300,000 R).

P.O. Makarov (1934) studied the ionising radiation effects on frog nervus ischiadicus *irritability, conductivity and refractory phase*. Neural-muscular apparatus was exposed to radon with 20–40 and 80–120 mCi. Under irradiation with 80–120 mCi the irritability and conductivity directly decreased and refractory phase shortened. Low doses (20–40 mCi) induced first the irritability and conductivity elevation, than — decrease and under long-term impact — parabiotic phenomenon.

D.A. Lapitsky (1935) with total roentgen exposure of frogs with 0.5–2 erythemal doses confirmed experiments by I.P. Tarhanov (1896) concerning *the strychnine convulsions arise onset* under the X-rays impact. But further the anticonvulsive effect of ionising radiation met no any practical verification.

E. Girden (1935) with conditioned reflexes method revealed the *acoustic analyzer* irritability depression.

V. Rascanu, M. Kapri, Ch. Popvichi (1938) revealed *chronaxy* increase under roentgen irradiation of dog cortex locomotive zone.

E.I. Bakin & A.N. Naumenko (1938) leadership of P.C. Kupalov conducted series of physiological studies of ionising radiation impact on *spinal cord and convulsore processes* that were of important role in nervous system radiosensitivity problem solution. In particular they demonstrated the underthreshold strychnine doses summation effect and radium emanation in convulsions genesis with further paralyses.

H. Davis & P. Davis (1939) for the first time applied the *electroencephalography (EEG)* method for ionising radiation effects on brain studies. Due to that they observed brain bioelectrical activity changes in exposed monkeys.

Elaborating the ideas of *ionising radiation reflex effect on central nervous system* possibility K.H. Kekcheev, Z.Z. Shajevich and A.P. Anisimova (1939) studied the *visual dark adaptation* under hands roentgen irradiation with 30–100 R doses. They revealed visual thresholds elevation under dark adaptation conditions with threshold effect of 30 R.

A.I. Naumenko (1939) demonstrated the *sartorial muscles zero signal currents* two-fold decrease in frogs after spinal cord lower segments irradiation from radium emanation preparations with activity 30–75 mCi. Zero signal currents almost not changed on the denervated body side.

E.I. Bakin (1939) determined hind extremities *skin permeability* to NaCl three-fold increase on body side with remaining innervation and one and a half-fold — on the denervated one in frogs with radon preparation (30–60 mCi activity) sewed to skin over the spinal cord lower segments. Author noted that irradiation evidently depressed *the spinal cord activity* as the spinal cord disintegration resulted in still more sharp disorders of skin permeability in respectively innervated zones.

V.A. Muzejev & E.I. Bakin (1939) revealed the *cross-striated muscles* structure disorders as cross-streaked pattern sharp alterations, homogenization and granularity arise after ionising radiation impact on spinal cord. No any alterations were present in denervated muscles.

T.I. Bakin (1941) observed *convulsions* in frogs after tubules containing radium emanation sewing up (15–50 mCi activity). Convulsions arose also after spinal cord irradiation but were not revealed after nervous fibers, skin and brain exposure. Spinal cord irradiation hastened strychnine convulsions rise.

Summarising the pre-war research results of his staff (E.I. Bakin, A.I. Naumenko, V.A. Muzejev) P.S. Kupalov (1959) noted that they on the contrary to other researchers for the first time received not the remote but direct acute radiation effect at the *specific effect*. Facts received within these studies *«...made penetrating radiation direct effect on nervous system presence almost undoubted»*.

R.R. Newell & W.E. Brley (1941) determined the threshold value of radiation dose rate required for *phosphen* rise as 0.5–1.4 $R \cdot min^{-1}$ per 1 mm^2 of retina. At that the threshold decreased with eye sensitivity elevation during dark adaptation process [Cited Motokawa K. et al., 1956].

M.I. Nemenov and V.V. Yakovleva (1942) revealed sharp decline of positive conditioned reflexes after roentgen irradiation of dog head with dose 1,500 R and after 4.5 and 10 months repeatedly with 1,500 R with exposure seance entailed by acoustic irritant (siren or metronome). Under similar irradiation mode but without acoustic irritant only the short-time depression of conditioned reflexes was noted. Thereto the same authors 1st irradiation seance authors initially noted the conditioned reflexes function improvement and further — the conditioned reflexes depression; after 2nd irradiation seance the nervous processes mobility deterioration was marked all after the 500 R impact on dog brain right and left hemisphere alternatively.

Less sharp disorders of conditioned reflexes function and radiation sickness clinical manifestations softness were observed by M.I. Nemenov and co-authors in dogs after repeated radiation exposures. Similar idea was stated by P.O. Makarov (1934) who underlined that observable alterations became less expressed under repeated radiation seances on isolated frog nerve. That gave background to issue the assumption concerning *«adaptation to radioactive effect»*. But U.G.Grigorjev was completely right noting further *«...ought to take into account that both with adaptation the cumulation process is taking place in repeated irradiation»* [U.G. Grigorjev, 1958]. That can be confirmed by works of M.B. Zuker (1942) who observed the cerebrospinal liquid absorption rate phase changes as the result of thrice-four-repeated roentgen radiation impact in low doses (160 R) on dog head.

A. Janzen & S. Warren (1942) revealed no irritability alterations after roentgen irradiation with 4,000–10,000 R dose of rat *nervus ischiadicus* i.e. that the threshold doses of ionising radiation inducing nervous function alterations may be rather high.

Thereby the high *radiosensitivity of central nervous system* and rather high *radioresistance of peripheral nerves* in human and animal were convincingly demonstrated with neuro- and psychophysiological studies in first part of XX century.

1.2.4. Ionising Radiation Impact on Autonomous Nervous System and Neuroendocrine Regulation

G. Rieker (1915) for the first time revealed disorders of *autonomous nervous system* after irradiation. G. Rieker (1915) & G. Gabriel (1926) initiated discussion about *parasympathetic nervous system* role *in hypotensive effect realization* after irradiation. Prophylactic effect of *acetylcholine, epinephrine, cholinolytics (ganglionic blocking agents) and cholinesterase antagonists* in radiation injuries was also discussed.

Data concerning *autonomous nervous system radiosensitivity* were stimulus for principally new radiation therapy method elaboration. In German literature in 1918 the information was presented about peptic ulcer successful treatment with X-rays. A.M. Ugenburg (1920) obtained the similar results. The same year M.I. Nemenov formulated the idea about favourable results possibility in various diseases management with ionising radiation impact on autonomous nervous system. O. Wolmershauser (1923), M.I. Nemenov (1928–1950) put forward the theory of *ionising radiation regulating effect on autonomous nervous system and through it — on organism in a whole.* M.I. Nemenov considered that ionising radiation normalising effect mechanism is linked to its selective impact on pathologically excited part of autonomous nervous system. Roentgentherapy was applied by M.I. Nemenov, A.M.sUgenburg and others for peptic ulcer, chronic constipation, long-term not healing fire-arm wounds, Raynaud's disease, frostbitten injuries, hypertension, angina pectoris, some endocrine diseases and traumatic psychoneuroses management. Considerable contradictions in just own study results interpretation by that concept authors is notable. Therewith according to the numerous literature data both with our own clinical observations results *«roentgentherapy through impact on nervous system»* is full of complications in remote period that were utmost not considered by authors.

O. Strauss & J. Rother (1924) observed blood pressure decrease from 65 down to 30 mm Hg. in rabbit after X-ray exposure in one erythemal dose. Blood pressure effect was absent in animals preliminarily injected with 0,1 g of atropine subcutaneously. At that in control experiments the injected atropine dose not induced blood pressure increase. In these refined experiments demonstrated blood pressure decrease absence after roentgen irradiation in atropine-treated animals, it was surely pointed at *central-nervous mechanism of roentgen-induced hypotonia* with *acetylcholine neurotransmitting systems* substantial role in its realisation.

V.V. Zakusov (1924) observed the *vascular reactions alteration* of rabbit isolated ear on some neurotropic agents directly during exposure to roentgen rays. Vasodilatation effect of caffeine after irradiation was more expressed than in control. Effects of preliminary injected epinephrine and nicotine were diminished or completely blocked.

N.A. Panov (1925) considered that *nervus vagus agitation* is basic for *«roentgen hang-over»* genesis after irradiation [Cited S.B. Darjalov, 1971]. Experimental works with nervus vagus cutting were presented for confirmation here.

N.V. Lasarev & A.P. Lasareva (1926), N.V. Lasarev & A.P. Lasareva (1926, 1927) demonstrated the skin vessels reaction on radiation relation to the vasomotor nerves functional status changes. They ascertained nerves-vasoconstrictors tone elevation 2 first hours after irradiation. Tone of nerves-vasodilators increased two days after exposure. Third phase took place four weeks later: vessels of irradiated ear more intensively reacted on vasoconstrictive drugs compared to vasodilative ones. These authors also demonstrated *vasomotor nerves tone phase-type alterations* after ionising radiation impact during study of radiation effect on inflammatory reaction.

N.V. Lasarev & A.P. Lasareva (1927) studied also the Roentgen rays effect on *capillaries and vasomotor nerves status* in human. They exposed the forearm of healthy volunteers to X-rays and in terms from few minutes up to one year after irradiation studied the vascular reactions on pharmacological agents and thermal irritants both on exposed and controlled sides. Authors revealed that within first hour after irradiation the vasoconstrictors irritability was elevated corresponding to spastic period. Irritability of vasodilators increased and vasoconstrictors — respectively decreases resulting in capillary dilatation one hour after the exposure to the 80–90% of erythemal dose. On the second day the phenomenon diminished but returned again correspondingly the 2^{nd} and 3^{rd} waves of erythema. Thereby the complete concurrency was fixed in these experiments between vasomotor undulatory tone deviations and erythemal reactions pattern.

H. Langer (1927) observed eye pupil dilatation and than — complete block of neck sympathetic nerve after it roentgen irradiation in cat.

J. Rother (1928) demonstrated no sugar content changes in of guinea pigs crushed liver tissue suspension after roentgen irradiation with doses in «5.9 times exceeding therapeutic ones». Also the roentgen rays made no impact on sugar content in dog isolated liver outflow liquid. Irradiation under the same conditions of liver in intact rabbit resulted in sharp hyperglycemia. At the same time no *roentgen hyperemia* was observed in four rabbits with denervated adrenals that indicated the *neuroendocrine regulation disorders* presence in radiation effects realisation.

Zimmern & Bert (1929) revealed *nerve irritability decrease, eye-heart reflex weakening and heart rhythm sharp changes* after roentgen rays impact with 2,000 R doses on separated vagal trunk.

G. Gabriel (1929) revealed *electrocardiogram alterations corresponding the vagal nerve tone changes* after roentgen exposure with 620–1,240 R on right side of rabbit neck with heart zone shielding.

R. Glauner (1933) proposed hypothesis about biologically active substances arose after ionising radiation impact are initially produced in autonomous nervous system and act not through the blood but through autonomous nervous system. *Sympathetic and parasympathetic ganglions both with vegetative nerves terminations* author considered «*the most important and main points of ionising radiation effects load point*». Along with biologically active substances production he assumed also the possibility of substances produced as well out of autonomous nervous system impact on peripheral nerves terminations. Thereby for the first time it was pointed out on *neurotransmittering and neuromodulatory brain systems* role in radiation pathology.

Among main statements in radiobiology there is the fact of *tissue initial status impact on their radiosensitivity*. S.A. Nikitin & E.P. Maksimchuk (1933) for the first time studied functional status of nervous system impact on organism reactions on radiation. Authors divided two phases of *experimental radiation sickness* in rabbits after roentgen exposure with 2,000–2,700 R dose. Initial «roentgenshock» was characterised with quickly increasing agitation arising 10–15 minutes after exposure and followed by depression, convulsive attack with bawl, urination and defecation, finally resulting in death 45–90 minutes after the irradiation. Authors considered the impact of toxic substances produced in irradiated organism on central nervous system being the cause of «roentgenshock». Final phase is the result of deep disorders of vitally important structures. Etheric-chloroform or magnesium narcosis applied during or after the irradiation prevented the *«roentgenshock»* rise reflecting its *neurogenic mechanism*.

M.I. Nemenov (1935, 1936) on the background of experimental and clinical observations came to conclusion that general initial reaction of organism on irradiation is the result of ionising radiation first phase impact on *autonomous nervous system* i.e. *elevated agitation* phase.

M.I. Nemenov & E.N. Mozarova (1938) observed *skin temperature changes* under roentgen exposure with 375 R doses of spine pectoral part and vegetative ganglions.

M.I. Nemenov, P.S. Kupalov, A.I. Naumenko and E.I. Bakin (1938) studied the ionising radiation impact on *respiratory center*. Radon preparation with 43–80 mCi activity was placed under the medulla in cat with removed hemispheres and thalamus opticus. Breath of animals became more frequent and deep 15–30 minutes after the exposure initiation and then animals died under *hyperventilation* symptoms.

A.V. Kantin (1938) observed alterations of stomach motility, gastric juice acidity both with eye-heart and breath reflexes after human neck exposure to radium preparation and roentgen rays with 1.5–2 erythemal doses. Under the similar conditions K.N. Chochia (1938) surveyed the carbohydrate and calcium metabolism alterations and at the same time — U.P. Arkussky & M.M. Mintz (1938) observed blood pressure decline with synchronous heart rhythm speed up and electrocardiogram alterations. Heart activity alterations the authors considered indicating *vagus and sympathetic nerves irritation* presence.

R.G. Gurevich (1938) observed *blood formula biases* (lymphocytes count decline and pseudoeosinophiles elevation) after thrice-repeated bilateral one-time irradiation of temporal lobes and parietal zone in rabbit with 312 R or 937 R doses.

E.A. Feldman (1939) observed body temperature elevation in human for 0.6–0.8°C and in one case — decrease for 0.5°C after X-rays 15% erythemal dose application on head. Author considered these effects as impact result on *brain autonomous nervous system centres*. Spinal cord exposure resulted in no any temperature elevation.

Ya.I. Geinisman, N.B. Mankovsky, A.A. Umansky (1939) revealed by means of biochemical study the ascorbic acid content alterations in brain hemispheres and cerebellum after roentgen irradiation with 4 erythemal doses of head in rat. At that they demonstrated that ascorbic acid content deviations are related not to its redistribution among the body but to its increased disintegration in brain tissue.

Ya.E.Shapiro (1941) revealed brain *trophic functions* sharp disorders under ionising radiation impact. After dog alternate bitemporal exposure to roentgen radiation with integral doses exceeding 2,700 R per 4–6 seances during 10–12 days he observed severe cachexia, hypoglycemia and sensitivity to insulin elevation.

M.I. Nemenov (1938, 1950) noted that sympathetic or parasympathetic effects after irradiation depend upon *the initial functional state* at he time of exposure. *«Radiant energy impact first of all involves nervous elements being in state of irritation»*. In other words human and animals with steady-balanced type of nervous system are more radioresistant than human and animals with unbalanced nervous system type.

Later E.I. Bakin demonstrated that *cortex irritated zones are in higher degree sensitive to radiation impact*. These data corresponded the results received by M.I. Nemenov, who observed more expressed striking effect in case of brain activity intensification with various irritants before irradiation. It is well known that *modifying central nervous system status before irradiation one can impact on its response reactions and radiation sickness process in a whole*. For instance in further U.G. Grigorjev (1958) demonstrated various initial state of central nervous system impact on progress of reactions observed directly during exposure.

Summary of pioneer study results in neuroradiobiology field is presented in Table 1.1.

Table 1.1

NEURORADIOBIOLOGY PROGRESS CHRONOLOGY (1896–1945)

Date	Discovery	Authors
1896	*Roentgen rays effect on organism*. First *neuroradiobiological* experiment. Possibility of roentgen rays application for *therapy*.	I.R. Tarhanov
1896	*Radiophosphen*	T. Edison, G. Brandes & E.Dorn

1896	*Direct behaviour reactions* on irradiation	Aksenfeld
1897	Radiation *neurological symptomatic* (pareses, paralyses, extremities trembling, tactile sensitivity disorders)	Uden, Bartelemy & Darjet
1901	Radiation *death* of organisms	Kinbeck
XX century beginning	General early radiation reaction — *«Roentgenkater»* — *«roentgen hang-over»*	German radiologists
1902	*Retina electrical reactions* under roentgen rays impact	F. Hishtedt & U. Hejgel
1903	*Brain cortex irritability* alterations after ionising radiation impact	M.O. Zukovsky
1903	*Cerebral vessels* radiation damage. *Young beings higher radiosensitivity* determination	J. Danich
1903	Radiation *morphological changes in neurones* of brain cortex	E.S. London, S.V. Goldberg, G. Gejneke
1904	Approval of *vascular disorders primacy* over neurones direct pathology in central nervous system radiation injury	V. Sholz, G. Obershteiner
1906	Radiation *development retardation* of organism	Forsterling
1906	Signs of nervous tissue *high radiosensitivity*	L.M. Gorovotz
1906	Determination of *«Bergonie & Tribondeau Radiobiological Law»* according to which nervous tissue is considered *radioresistant*	J. Bergonie & L. Tribondeau
1913	*Peripheral nerves functional state* radiation alterations	V. Lasarus–Barlow
1915	*Autonomous nervous system* radiation disorders. *Autonomous nervous system high radiosensitivity* determination. *Parasympathetic* nervous system role in radiation *hypotensive effect* realisation. *Neurotransmitters* effect for radiation injuries prophylaxis.	G. Riker
1918	Radiation *epileptiform attacks*	G. Brunner & G. Shvartz
1920	*Cerebellum* radiation damage	G. Brunner
1922	Peripheral nerves radiation *demyelination*	E. Redfield, A. Redfield & D. Forbs
1922	Radiation *toxaemia*	Pendegrass et al.
1923	Theory of ionising radiation *regulating effect* on autonomous nervous system and through it — on organism in a whole	O. Valmershauser
1924	Radiation *hypotonia* central-neural mechanism	O. Shtrauss & J. Roter
1924	*Vestibular analyser* radiation injury	K.L. Hilov
1926	*Vasomotor centres* radiation alterations phase nature	N.V. Lasarev & A.P. Lasareva
1926 - 1927	Central nervous system radiation injury as the result of *prenatal irradiation* after pregnant women roentgentherapy	J. Zappert, M. Robinson
1928	*«Roentgentherapy through effect on nervous system»*	M.I. Nemenov
1928	Radiation *hyperglycemia*. *Neuroendocrine regulation* disorders role in radiation effects realisation.	J. Roter
1929	Skin *nerves terminations sensitivity* radiation alterations	M.S. Lutershtein & A.V. Rahmanov
1930	*Blood-brain barrier* radiation injury	B.N. Mogilansky & L.D. Podlaschuk
1932	Radiation *psychophysiological effects* (conditioned reflexes alterations)	M.I. Nemenov
1933	*«Roentgenshock»* neurogenous nature in experimental radiation sickness. *Initial tissue state* impact on their radiosensitivity	S.A. Nikitin & E.P. Maksimchuk
1933	Radiation degenerative alterations in *cortex and subcortex diencephalic ganglionic neurones* and atrophy degenerative processes in neurones of *lateral and back horns of spinal cord* (in young beings)	D.G. Shefer
Date	**Discovery**	**Authors**
1933	*Vascular and neuronal* radiation injuries combination in brain. *Higher nervous function type* role in nervous system reactions on irradiation	R. Lyman, P.S. Kupalov & V. Sholz
1933	Radiation alterations of *psychics in children* (memory and attention abatement)	G.N. Avergetova, S.I. Zindberg & R.V. Gorainova
1934	*«Adaptation to radiation impact»* hypothesis	P.O. Makarov
1936	*Autonomous nervous system ganglionic cells* recognition as nervous system most radiosensitive elements. Radiation alterations of *cerebrospinal liquor* production	D.G. Shefer
1936	First *radioneuroembriological* experiments	A.A. Zavarzin et al.
1937	Radiation *necroses in brain parenchyma* after roentgentherapy application	J. O'Connel & A. Brushvig
1938	Radiocerebral effects dependence on irradiation *dose* determination	L.M.Davydov et.al.
1939	*EEG* first *application* for radiocerebral effects study	G.Davis & P.Davis
1939	First *radioneuroimmunological* studies	R. Alderhalden
1941	Radiation alterations in *heart and neck sympathetic ganglions neural elements*	I.M. Zdanov
1942	Higher nervous function disruption and *«neurotic state»* rise after irradiation	M.I. Nemenov & V.V. Yakovleva
1942	Irradiation effects *cumulation*	M.B. Zuker

Thereby already in first part of XX century the autonomous nervous system high radiosensitivity was surely demonstrated both with neuroendocrine regulation role in organism reactions on irradiation.

The first i.e. investigative period of radiation neuropsychiatry was characteristic with experimental and clinical data accumulation concerning effects of «Roentgen and radium rays lighting» of nervous system and organism in a whole. Scientific heritage of this period is of extreme value enabling to consider the ionising radiation neuropsychiatric effects problem separately from psychogenic reactions after extreme situations.

Clinical observations were presented with ray therapy and roentgendiagnostics consequences both with occupational exposure of roentgenologists, experimentalists and workers being in contact with radioactive isotopes. At that for long time the dependence of disorders on radiation impact remained unclear. Various manifestations of those disorders (somnolence, headache, nausea etc.) were first connected to mental disorders and in further — to intoxication by nitride gases and ozone produced in workrooms with roentgen facilities. Only later on with radiation technologies and radiobiology progress it was revealed that those disorders are in causal dependence upon radiation impact.

Many authors on the background of experimental studies results denied possibility of mature nervous tissue radiation structure alterations, and in case of those alterations nevertheless been observed after massive doses application, still considered them the secondary results of circulation disorders. At the same time the following statement was presented in Mayer's roentgentherapy handbook in many volumes (Chapter written by Heineke & Pertes): «Central nervous system with both ganglionic cells and nervous fibers with neuroglia at any rate in adult animals and human undoubtedly are referred to the list rediosensitive organism elements. As far as we know from experimental and clinical studies results the alterations in brain and spinal cord may occur under doses in many times exceeding those applied in roentgentherapy i.e. dose values resulting in disorganisation of any living tissue. Exactly the same way central nervous system do not functionally respond to therapeutic doses» (vol. 1, P.791) [Cited M.I. Nemenov, 1950].

Though the majority of roentgentherapists and histologists held the positions presented above the principally opposite opinions existed. Thus M.I. Nemenov (1928, 1935, 1938, 1950) considered radiobiology followed the wrong path been keen of morphological direction. As the result the nervous system occurred being out from field of vision of radiobiologists and *«...the wide range of rather important alterations arising in organism after roentgen rays lighting was regarded not to the nervous system primary disorders but to the toxic phenomenon as the result of organism inundation with cell disintegration products»*.

In conclusion it is necessary to note the scientific baselessness of «morphological» and «functional» contraposition of radiocerebral effects that is continued at present time. Contradictoriness of diseases dichotomy into «functional» and «organic» ones is laid in the definition «functional» itself — it means the external manifestation of somewhat structural property. As absolutely rightly noted D.S. Sarkisov (1994) the structure and function as one manifestations of the matter and movement present two amalgamated together sides of vital function. Previous opinion about functions higher lability than structural one and those of functional alterations surpassing character compared to morphological ones nowadays is the anachronism. Modern level of knowledge about living matter provides background to state flatly that no any even the finest functional cell alterations cannot take place without respective structural disorders on subcellular level.