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STUDIES ON IRRADIATION SICKNESS IN THE USSR

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1. The Dynamics of the Pathological Process in the Nervous System of Individuals Subjected to the Protracted Influence of Comparatively Small Irradiation Doses

The basic source of our concepts on the reactions of the nervous system to the protracted influence of comparatively small irradiation doses in the practice of roentgenotherapy of functional, infectious and, to a lesser extent, neoplastic diseases of the brain which has been carried on for many years (A. V. Kozlova; M. I. Nemenov; M. N. Pobedinskiy; Bente and Schneider; Ellinger; Dyke and Davidoff; and others), as well as the results of observations of individuals who have been subjected to irradiation under laboratory conditions (workers of roentgenoradiological consulting rooms, γ-defectoscopists, individuals, attending accelerators, etc.) (V. V. Blagoveshchenskaya; E. A. Drogichina and co-workers; M. A. Kovnatskiy and co-workers; L. M. Omel'yanenko; T. S. Seletskaya; I. Ya. Sosnovik; P. D. Sidrer and Ye. G. Teselkina; M. N. Fateyeva and co-workers; F. A. Effendiyev /reference not given/).

The data of experimental investigations present considerably less information in this respect (N. Ye. Kuznetsova, M. S. Lapteva-Popova; A. V. Lebedinskiy and co-workers; M. N. Livanov; I. N. Molokov, A. G. Khanin, N. Ye. Kuznetsova and Kh. Kh. Yarullin; I. A. Pigalev; S. A. Rogacheva, N. P. Kudasheva, T. V. Oliper and Z. I. Kalmykova).

The comparison of all these more or less complete pieces of information and their discussion represents an extraordinarily important task at the present stage of development of radiation neurology. Such a comparison, being reinforced by certain data of experiments close in conditions to clinical practice, at the present time permits us to pre-

sent a rather complete general scheme of the dynamics of the process in the nervous system in the presence of the protracted influence of small irradiation doses, the increase in the total levels of which can already lead to the formation of various syndromes of chronic radiation disease.

The well-known differences in the character, sequence, and frequency of the deviations which are revealed when the data of different authors are compared are determined, as a careful analysis shows, basically by the failure to coincide of the single time and total doses and the irradiation conditions.

The results of numerous investigations, beginning with the works of the first Russian radiobiologists (M. I. Nemenov) and ending with the investigations of the last few years (Ya. I. Geynisman and Ye. A. Zhirmunskaya; A. V. Lebedinskiy; M. N. Livanov; I. M. Velikson /separate reference not given; see Kovnatskiy, Makulova, and Velikson/) have directed the attention of scientists at the search in the clinical neurological picture of radiation injuries for signs of change in the physiological reactions to adequate stimuli. Such signs in the general form include all forms and degrees of change of the height, latent period, and duration of the diverse reflexes, by means of which the organism constantly balances its activity with the changing conditions of the medium.

As the majority of literature data attest (V. L. Baranov /reference not given/, E. A. Drogichina and co-workers; Ye. V. Yermakov /reference not given/; E. A. Drogichina and co-workers; Ye. V. Yermakov /reference not given/; M. A. Kazakevich; M. A. Kovnatskiy and co-workers; V. I. Kuznetsov and co-workers; N. A. Kurshakov and I. S. Glazunov; A. V. Lebedinskiy; M. N. Livanov; and others) soonest of all there arise disturbances in the reflex activity which are reflected in the state of the internal organs. Later (in the presence of a greater duration and greater total radiation doses) initially functionally, and then anatomically the systems of other analyzers -- particularly the motor analyzer -- suffer.

In the presence of the prolonged action of comparatively small irradiation doses, the changes of the nerve centers are occasioned to a lesser by direct injury and to a considerably greater extent arise reflexly as a consequence of stimulations, flowing from all the irradiated organs and tissues. However, in the presence of any method of involving the nervous system in the reaction to the action of irradiation, the involvement proceeds very early and at the same time, as the investigations of M. N. Livanov; Yu. G. Grigor'yev and others have shown, follows the general patterns of

dynamics of neural processes in the presence of the action of any stimuli.

As follows from a number of morphological investigations (Ch. Berens /reference not give; A. F. Bibikova; N. A. Krayevskiy; D. G. Shefer; Marburg /reference not given/; Wachowsky and Chenault /corrected misprint/), the anatomical integrity of the nervous system is retained for a rather prolonged period in the presence of the influence of extremely small irradiation doses. This is particularly regularly true for adult individuals with completed organogenesis of the nervous systen when the irradiation doses are comparatively small.

Observations of the dynamics of the symptoms in the presence of X-ray therapy (M. P. Domshlak and co-workers, A. V. Kozlova; M. I. Nemenov; D. G. Shefer and others), materials of certain experimental physiological (M. N. Livanov; Ya. I. Geynisman and Ye. A. Zhirmunskaya; Yu. G. Grigor'yev), histological (D. G. Shefer; D. G. Shefer; V. V. Portugalov /reference not given/; A. A. Afrikanova /reference not given/; A. F. Bibikova) and other investigations provide every basis for assuming that the initial reaction of the nervous system to irradiation is manifested in the form of displacements of the functional activity of the neuron such as the early arising changes in the hemo- and cerebrospinal fluid dynamics of the brain, associated with disturbances in its glialo-vascular apparatus. These last disturbances are reflected in their turn in the conditions of existence of the neuron. Thus, judgment concerning the strict demarcation of these two components of the initial reaction is to a considerable extent conditional. From the point of view of the general biological patterns the earlier involvement in the pathological process of such reactive structures, as various kinds of glia, the myelin of the conducting routes, the cellular elements of the peripheral vegetative ganglia and then the ganglion formations of various regions of the brain themselves also becomes understandable.

It should be indicated, that no strict specificity exists in the primary clinical manifestations of the reaction of the nervous system to the protracted action of comparatively small irradiation doses; this is also the case in the presence of other unfavorable general pathological and occupational factors (mercury, lead, benzene, vibration, etc).

When the biological effects of radiation are cumulative, in the first place there is noted the appearance of sympton of variously directed fluctuations in the activity of a number of organs and systems, exceeding the physiological fluctuations; then there arise signs of exhaustion of their functional possibilities, and only later do anatomical changes occur in

the structures of the nervous tissue. This position, confirmed by the comparison of the frequency and intensity of the various neurological syndromes with the intensity and total dose of irradiation (M. P. Domshlak with coworkers; M. A. Kovnatskiy and co-workers; I. D. Makulova /reference not given; see Kovnatskiy, Makulova and Velikson/; and others) permits one to distinguish three basic neurological syndromes of chronic radiation sickness which successively replaces each other: 1) the syndrome of disturbance of the neuro-visceral regulation; 2) the asthenic syndrome; 3) the syndrome of organic injury of the central nervous system.

The first of the indicated syndromes, which is also being diagnosed by various authors as a syndrome of disturbance of the neuro-vascular regulation, vegetative-vascular dysfunction, neurocirculatory dystony of a hypotensive type, is most characteristic for the initial phases of the reaction of the nervous system and the organism as a whole to the prolonged influence of comparatively small irradiation. A clean-cut increase in the frequency of this syndrome (in comparison with the presence even in control observations of a definite quantity of individuals with an excessive lability of the neuroregulatory processes) proceeds only when a certain threshold level of the radiation doses is achieved.

This syndrome was observed more regularly in individuals who had been subjected for the course of a prolonged period (two to three years) to the influence of irradiations in doses equal to 0.2 - 0.3 r per day (γ-defectoscopists, who were under observation by the co-workers of the Leningrad and Moscow Institutes of Labor hygiene and Occupational Diseases). The clinical picture is less clearly outlined in those cases in which an exceeding of the limiting permissible levels of irradiation were not successfully registered (A. V. Kozlova; M. N. Fateyeva with coauthors).

In the analysis of the literature data the definite impression is sometimes created of the lack of basis for classifying any manifestations of disturbances on the part of the nervous system as consequences of radiation influence in the presence only of indications to the effect that these individuals had "some sort of" contact with radioactive materials (S. A. Kogan; I. Ya. Sosnovik).

A final solution of the problem of the specificity of the initial neurological symptoms, their connection with the action of radiation and of the threshold doses, necessary for their arising, is complicated by the fact that the clinical, neurological, and physiological investigation under experimental conditions, particularly on large laboratory animals, has been conducted extremely rarely (T. V. Oliper /reference not given; see Rogacheva, Kudasheva, and Oliper/; S. A. Davydov /reference not given/; I. M. Molokov and A. G. Khanin).

However, preliminary discussions can nonetheless be expressed on the basis of an analysis of the available observations.

Thus, it is well known that a certain regular and statistically reliable increase in the frequency of the above described disturbances of the neuro-visceral regulation in man sets in only when the daily limiting permissible dose, accepted until very recently (0.1 r/day) is exceeded by two to four times and when the total levels of influence approximate 50-100 r of external irradiation. The fluctuations of these levels in the experiments on dogs were also comparatively small and approximated 80-120 r of the external irradiation. There is practically no convincing information in the literature concerning the threshold quantities of radioactive substances leading to the development of these initial forms of reactions of the nervous system.

The clinico-physiological characterization of the syndrome of disturbances of the neuro-visceral regulation (and its symptoms) is rather fully presented in the literature. This syndrome is diagnosed on the basis of signs giving evidence concerning functional changes in the nerve centers themselves, and also indicating a change in the usual level of activity of the internal organs. The anatomico-physiological peculiarities of the vegetative-visceral innervation, and also the great number of applications of stimuli to various divisions of the reflex arc, occasion a considerable multiplicity of the clinical manifestations of the initial period of chronic radiation sickness with the involvement in the pathological process of a number of organs and systems. However, by virtue of the physiologically higher lability of the vascular system, symptoms of disturbance of the neuro-vascular regulation appear to be dominant in the early periods.

The clinical picture of the initial phases of radiation sickness is also made up basically from the changes in the capillary circulation in the skin occasioned by disturbances of the nervous regulation, spasm or atony and stasis in the main and smaller vessels of the extremities and brain, diverse fluid /i. e., of the CSF/ hydrodynamic disturbances along with other vegetative-visceral shifts. The characteristic headaches, of the paroxysm-like migraine type, are localized in definite regions, often arising in the presence of any loading; later the pains become more constant. Sometimes a moderate dyspnea and vertigo are noted, also, as a rule, associated with physical loading or with change in position. Complaints of a reduction in appetite, pains in the region of the stomach and intestine are encountered more rarely. In objective investigations of these patients there is noted a nonacute lability of the pulse, fluctuations in the height of the arterial and fluid pressure, changes in the capillary blood flow

with alternation of phenomena of spasm and atony and shifts of the vascular reactions to diverse stimuli in the direction both of hyporeactivity, and also of hyperreactivity.

In the neurological status there are manifested unstable systemic or focal symptoms, most often an asymmetric rise in the tendon reflexes, a lowering of the skin reflexes, light locomotor disturbances, inconstant oculomotor disturbances and nystagmus. Transient vestibular or oculovestibular and oculostatic disturbances are characteristic. At the same time, vestibular tests do not as a rule reveal substantial signs of injury of the trunk nuclei or of the periphery of the vestibulor analyzer itself. The vestibular reactions proper (postrotatory and postcaloric nystagmus) are weakened more quickly and shortened in time. However, the vegetative component of the reaction is significantly expressed.

The predominance of hydrodynamic disturbances of the fluid is most often observed in the clinical picture in individuals who have not only undergone overirradiation, but who have also been subjected in the past to one or another infectious or traumatic disease of the central nervous system. These disturbances in the fluid hydrodynamics are occasioned by systemic and limited disturbances in the arterial and venous blood flow in the brain and its choroid plexuses, by venous stasis, hampering the outflow of fluid, by systemic shifts in the water-salt metabolism (hypochloremia) and, finally, by degenerative changes in the epithelium of the choroidal plexuses and the oligodendroglia, which have been ascertained in experimental-morphological investigation of radiation sickness very recently (A. F. Bibikova; D. G. Shefer and others).

All the symptoms enumerated above, as also the entire syndrome of disturbances of the neuro-visceral regulation, are a functional-dynamic form of the reaction of the nervous system, in many respects reversible in the present of the opportune ceasing or significant lowering of the levels of radiation influence to the limiting permissible levels. The connection of the symptoms with the changes of the functional level of the nerve centers and with disturbances of the intracranial hemodynamics and fluid hydrodynamics is confirmed by a definite correlation of these two groups of phenomena, by the lability and dynamism of the symptoms, and also by the effectiveness of the corresponding therapy (dehydrational and normalizing the neural and vascular tonus).

Varying direction and inconstancy of the shifts of function of the organ, not so much predominant disturbance of the spontaneous level, as the possibility, manifested in the presence of definite loading, of modifying the force, duration, and time of arising of one or another reaction by

the application of the corresponding neurotropic agents; the prolonged satisfactory compensation of the deviations which are present; all are also characteristic of all other visceral disturbances in the early phases of the disease.

The data of certain special electrophysiological investigations (chronaximetric, electroencephalography) confirm the clinical notions concerning the character of the functional shifts in the nerve centers which lie at the basis of the above described syndrome of disturbances of the neuro-visceral regulation. At the same time there is manifested an unstable asymmetric increase in the chronaxy of the extensors which changes after taking caffeine, a tendency toward an increase in the chronaxic coefficient, an unequal lowering in the reaction of the biocurrents of various regions of the cortex to the action of an adequate stimulus, the distortion of the ratios between the intensity of the reaction and the force of the stimulus, the presence in the electrocorticogram of acute high waves, often synchronized with the rhythm of the pulse.

As has already been indicated above, the next phase in the reaction of the nervous system to the prolonged action of comparatively small irradiation doses is the asthenic syndrome, characterized by a further lowering in the functional activity of the nervous system and in the level of activity of the organs. The simultaneous, although unequal in degree of intensity, injury of various levels of innervation of the working organ itself imparts a considerable severity and stability to all manifestations of the indicated syndrome in the presence of the action of radiation.

Complaints of stubborn dull aching headaches, most often in the frontal region, which arise or intensified in the second half of the day, after earlier physical or mental loading has been undergone well are characteristic. Prolonged stress of the attention, hearing, sight, i. e., any stress of the process of active inhibition, evokes pronounced emotional-affective reactions. Sluggishness and "hypomimia" arise; the motor activity is diminished. A general physical weakness and a raised fatiguability are noted. A reduction in weight and disturbances in sleep are observed. Subsequently, particularly in the presence of supplementary unfavorable emotional-physhic factors, there arise stimulability, emotional faint-heartedness; typical neurotic reactions are possible, most often of a neurasthenic character, in noncomplex conflict situations. In subsequent periods of observation, objective signs of shifts of the higher nervous activity (particularly in the interaction of the first and second signal systems in the presence of the formation and strengthening of the conditioned reflex) are more regularly noted. The physiological

interaction of the olfactory and the visual analyzers, and also, apparently, other afferent systems, is distorted or weakened (V. V. Blagoveshchenskaya).

The greater frequency and intensity in the presence of the asthenic syndrome of various deviations in the neurological status also appears to be an index of the increasing reduction in the activity of the nerve centers. The general muscular hypotony, particularly noticeable in the lower extremities at rest and in the recumbent position, static ataxia, light locomotor disturbances are characteristic. After the initial increase in the tendon and periostal reflexes with widening of their reflexogenic zones in a portion of the cases a certain irregular lowering of them is noted. An asymmetric or uniform lowering of the abdominal reflexes, which have, as a rule, already a comparatively stable character, is relatively often encountered. Various disturbances in the sensitivity, although not strictly outlined, are manifested, most often vibrational, lesser and more rarely superficial. Changes arise in the reception of optimal and least favorable frequencies of impulse stimulation /and/ diverse dysesthesias /arise/ which spread the vegetative reactions to pain stimulations.

In the presence of an electroencephalographic investigation there is observed a further weakening and distortion of the reaction of the cortex to light stimulation: the threshold of the reaction is raised and becomes indistinct, the phasicity and correct correlations with the force of the stimulation are disturbed, the latter becomes more prolonged. No substantial improvement in the spontaneous cortical activity and reactivity is successfully achieved when caffeine is prescribed. In a chronaximetric investigation with a considerable frequency there is manifested a lowering of the "flexor/extensor" coefficient with approximation of it to one, which is evidence of a distortion of the reciprocal physiological correlations in the innervation of these two antagonistic muscle groups.

The state of the internal organs is also characterized by a further intensification of the disturbances in their activity; however, at this phase the disturbances are still in many respects of a functional character (V. I. Kuznetsov and G. A. Luk'yanov; N. A. Kurshakov; P. M. Kireyev; A. L. Morozov, E. A. Drogichina, M. A. Kazakevich and N. I. Ivanova). Signs of functional insufficiency of the internal organs are most clearly manifested when definite loads are applied to them.

Many peculiarities of the reactions of the internal organs, the nervous system, are successfully modified even in these periods by the application of various cortical and

vegetative stimulators. This once again indicates a predominant disturbance not of the executive peripheral apparatus, but of the intermediate neurons of the reflex arc and of the central sections of the analyzers, and also indicates a satisfactory intactness of the nervous system itself and considerable possibilities of compensation for disturbed functions even in comparatively late periods of the disease.

The clinico-physiological characteristics of the phase of organic changes in the nervous system in the presence of chronic radiation sickness have been least adequately illuminated in the literature. At the same time, the accumulation of experience in the use of large doses in the presence of local and total X-ray therapy (M. P. Domshlak with coworkers; A. V. Kozlova; Dyke and Davidoff; Freynd and Davydov /Friend and Davidoff; reference not given/; Shol'ts and Khau /Schultz and Howe; reference not given/; Viten /Whiten; reference not given/; and others), and also of the comparatively prolonged exceeding of the limiting permissible levels of irradiation under conditions of poorly equipped X-ray radiological rooms (A. V. Kozlova, K. M. Malenkova, Ye. K. Karibskaya and T. S. Seletskaya; Krabenhaft /reference not given/) and of certain industrial specialties (M. A. Kovnatskiy and co-workers; L M Omel'yanenko) shows that the transition from functional changes in the nervous system to anatomical changes is quite possible.

Individual stable symptoms, included in the lowering or the falling off of one of the tendon reflexes, the asymmetry of the skin reflexes, the muscular hypotony, the statico-coordinator disturbances, the nystagmus, are also encountered in earlier periods in individuals who had been subjected to the prolonged radiation influence in doses exceeding the limiting permissible doses. We assume, however, that one should diagnose the syndrome of organic injury of the central nervous system in the presence of radiation influence only in the presence of the reliable exclusion of other possible causes (trauma, infection) and in the presence of a definite complex of symptoms, most often involving the motor and reflex and to a lesser extent the sensory spheres. Most often in the clinical picture these disturbances bring to mind gently proceeding forms of disseminated demyelinizing encephalomyelitis (disseminated sclerosis) or funicular myelosis.

When observing the dynamics of the symptoms in comparison with the dose one can note that the changes in the height and tonicity of the tendon and skin reflexes, the light statico-coordinator disturbances, the nystagmus set in earlier, while the muscular hypotony and the disturbances in the vibrational sensitivity set in later. Such a sequence of symptoms

indicates that changes in the conducting systems of the lateral and anterior columns and the brain stem arise earlier and changes arise later in the posterior columns and cerebellar peduncles. This representation is in full accord with the data of physiological and morphological experimental investigation, which indicates the predominant injury of systems conducting the nerve impulses at the level of the brain stem and the spinal cord, in the presence of the prolonged absence of anatomical changes in the peripheral motor neuron and neural elements of the cortex. It is possible, that cases of the selective or uniform deposition of certain radioactive substances (strontium, tritium, cesium, etc.) will be a certain exception to this rule; for these radioactive substances, according to toxicological data (Yu. I. Moskaleva /reference not given/; I. A. Pigalev; M. N. Pobedinskiy), one can expect a somewhat different localization of the predominant injury.

The progression of the process in the presence of radiation sickness should lead to a further increase in the changes in the structure of the neurofibrillar apparatus of the fibers and cells, in the myelin of the conducting routes both of the previously injured, and also of the new regions of the nervous system, and should lead to the development of secondary glial reactions in the vicinity of these foci. The intensity and severity of all the changes in the nerve elements proper in the later periods is rendered more profound by injury of the vascular network of the brain, which acquires the character of changes which bring to mind those in the presence of atherosclerosis.

At the same time, the transient type of changes in the structure of the neurofibrillar apparatus, the well-known reversibility of the demyelinization process, and also the possible mechanisms of compensation for neuro-vascular disturbances lie at the basis of the definite lability of the clinical symptoms even in the phase of organic injury of the nervous system in the presence of chronic radiation sickness.

The data of clinico-physiological observations show that the period of complete falling off of the central regulating influences on the peripheral neuron in the presence of the influence of radiation precedes the prolonged (particularly in the presence of small irradiation doses) period of unequal irritation of the nerve centers and of disturbance of the inter-center correlations. Such a pathogenetic conception ensues from the clinical data concerning the presence of a period of prolonged general intensification of the reflexes, an equalization of the reflexes from the flexors and the extensors, a shortening of the chronaxie of the muscles

with approximation of the chronaxic coefficient to one, a lowering of the thresholds of various analyzers to the initial periods of formation of the syndrome of organic injury of the central nervous system. The intensity of the reflex reactions is later diminished. There takes place not only an increase in the chronaxie, but also sometimes a considerable increase in the rheobase of the muscles, the spectrum of the basic frequencies of the spontaneous bioelectric activity of the cortex is changed (the less frequent and more frequent rhythms predominate in the presence of a falling off of the middle frequencies -- those eight to ten per second). There is created a definite systematicality, a selectivity of injury in the presence of signs of restoration of the activity of other centers which had suffered less.

However, when the radiation influence ceases or is even significantly lowered to the limiting permissible level, the organic defect which is present for a long time remains satisfactorily compensated for. A particularly clear-cut and stable compensation, even in the absence of regression of the organic neurological symptoms themselves, takes place in the outcome of former earlier radiation influences in individuals who had not been burdened with any other nervous or general somatic diseases. Age exerts a definite influence on the degree and completeness of restoration; the reparative processes are more pronouned in young individuals.

In the presence of protracted influences, the syndrome of organic injury of the nervous system is usually combined with the asthenic syndrome and is complicated by pronounced disturbances of the circulation, which considerably diminishes the possibilities of compensation. It should be noted that reliable cases of the development of cases of paresis, paralysis, pelvic disturbances and other signs of profound decompensation of the existing organic defect have not been described up to the present time even in the presence of a more prolonged systemic influence of comparatively small radiation doses.

The gradual increase in the dystrophic changes of the internal organs, particularly after massive local X-ray influences, and also local irradiation with large doses of the brain itself can unconditionally substantially change the above-described classic scheme of the dynamics of the neurological symptoms in the presence of chronic irradiation. In these cases a special stability and intensity of certain deviations is noted, which already have in many respects a secondary character or depend on direct injury of the nerve centers. A special role in this connection apparently belongs to general and limited disturbances in the circulation.

It is precisely this characteristic insufficiency of

the vascularization and the hypoxic state of the tissue occasioned by it which in many respects determine the stubborn cerebrasthenic phenomena which are observed in the later periods and which apparently lie at the basis of a number of organic neurological symptoms, including the ostalgic syndrome. The characteristic clinical manifestations of the latter -- the maximally frequent localization of pains in the legs, the increase in the pains at rest and their diminution in the presence of motions, the hypothermia, the presence of pronounced signs of disturbance of the circulation in the capillary, arterial, and venous blood flow, particularly of the lower extremities, in combination with the earlier signs of predominant injury of the vegetative ganglia, the lateral and posterior columns of the spinal cord -- appear to be one of the examples of similar combined neuro-vascular disturbances in the clinical study of the late radiation injuries.

There are no descriptions in the literature of profound anatomical changes in the nervous system which appear to be the basic cause of the fatal outcome in patients with chronic radiation sickness. The neurological syndromes which are observed in the terminal period in individuals subjected to the influence of radiation and who perished from leukosis or hypoplastic anemia, complicated by various infectious processes (V. G. Piskunova and A. M. Vychegzhanina; N. I. Shcherbakov /reference not given/) appear unconditionally to be nonspecific for chronic radiation disease.

The increase in the duration of observations of individuals subjected to the prolonged influence of small radiation doses will possibly lead to the detection of some other forms of late manifestations of injury of the nervous system, and also of certain other rarer syndromes, which are observed in the early periods. However, it will apparently not introduce substantial changes into the general scheme presented above of the development of clinical neurological manifestations in the presence of the prolonged influence of radiation.

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2. Errors in the Diagnosis of Chronic Irradiation Sickness

Errors in the diagnosis of chronic radiation sickness can arise either on account of overestimation of the significance of the radiation factor in the development of the disease state, or of underestimation of its role, when the possibility of a pathogehetic influence of the irradiation which has occurred for some reason remains unobtrusive and consequently unconvincing. There is no doubt that both the combined influence of the radiation factor and extraneous noxious factors can hamper the "cleanness" of the clinical picture as a consequence of which a confused clinical picture is observed and the physician either overestimates or underestimates the significance of the irradiations.

The problem is further complicated by the overestimation of the principles of the threshold nature of the influence of irradiations, /and/ of the role of the limiting permissible doses. The significance of the latter is completely relative; consequently in all countries there is observed a tendency toward lowering them. The erroneousness of overestimating their role and, consequently, the complacency of the physician in the presence of the information available to him concerning the absence of exceeding the limiting permissible doses on the part of the patient depends, in the first place, on the insufficient taking account of the entire complex of irradiations received, for example, the calculation only on the basis of the γ-irradiation without taking account of the neutrons; in the second place, on the underestimation of the summation and cumulation of the sequelae of irradiations in the presence of repeated influences on the organism, already changed in its reactivity by preceding influences; in the third place, on underestimation of the disturbances in the adaptation of the organism to the irradiation to which it has been exposed; in the fourth place, on underestimation of the individual sensitivity and reactivity of individuals to the radiation received (as also in the presence of any other stimuli), which sometimes occasions completely inadequate sequelae from the irradiation doses received.

In evaluating the state of health of the individuals being investigated one should pay attention to the influence of climatic factors on the conditions where the individual lives, to the influence of special so-called local peculiarities, fro example, endemic diseases, deviations from the generally accepted norms of indexes, for example of the blood, the endocrine system, hemodynamic ratios, etc.

There is no need to repeat that the evaluation of the phenomena being observed at the present time acquires great

significance, if their indexes are compared with the indexes noted earlier, for example, before going to work, before having undergone one or another disease, etc.

Thus, errors in diagnosis can have the most diverse causes. To eliminate them an excellent clinical preparation of the physician, his knowledge of the general and production medical history of the patient being examined, familiarity with the conditions of his life work, and living conditions are required.

One can present a number of examples to illustrate what has been said.

A worker entered the polyclinic who had earlier been healthy. Instances in which the influences of the permissible radiation doses were exceeded were not registered for him. However, in view of the suddenness of the appearance of the signs of disease (chills, headache, nausea, inclination to vomit) and the requirements of the polyclinic, the dosimetric service undertook a supplementary investigation of the working locale, which took several days.

The state of the patient was of medium severity. The temperature was 38 to 38.5°. There was tachycardia, hyperemia of the skin and of the mucosa of the pharynx. No injury of the internal organs was determined. The number of leucocytes reached 10,000 to 12,000 with relative lymphopenia. Toward the end of the second day to the beginning of the third day, the state of the patient improved; the temperature became subfebrile, the hyperemia of the integuments was diminished, the number of neutrophiles reached normal, the lymphopenia remained. Scarlet fever eruptions were clearly manifested on the fourth day. The dosimetry data established precisely that the irradiation dose had not been exceeded.

Similar errors or doubts are possible when precise information concerning irradiation disease and convincing data concerning the presence of infectious disease is absent. The blood of the patient could have corresponded in its composition with that of a patient at the beginning of radiation sickness.

An electrician by occupation, he had been subjected to the influence of radiation in doses sometimes exceeding the limiting permissible dose for the course of two-and-a-half to three years. When treated in the polyclinic in connection with a worsening in the way he felt and an increase in the asthenic complaints, the patient concealed from the physician disease with fresh primary syphilis and the fact that he had passed in this time a course of massive antiluetic therapy, including arsenic. The arising of asthenic manifestations, and also of significant changes in the picture of

the peripheral blood (leucopenia, neutropenia with a simultaneous stabnuclear /palochkoyadernyy/ shift, moderate thrombocytopenia) and of the bone marrow in combination with information concerning what had taken place, in spite of the insignificant overirradiation, gave grounds for the diagnosis of chronic radiation disease. The stability of the symptoms, and also the appearance of signs of organic injury of the central nervous system, in spite of the prolonged transfer of the patient to "clean" conditions, in the presence of a comparatively small total dose of irradiation, forced one subsequently to doubt the etiology of the deviations which had been detected. Then making the medical history more precise, the refusal of the arsenic therapy and the transfer to the ordinary antitoxic and antisyphilitic treatment with excellent effect provided a basis for rejecting the incorrect diagnosis and evaluating the symptoms which had been observed as one of the characteristic complications of antisyphilitic treatment with a very toxic preparation on the background of early neurosyphilis.

A female technician was subjected to the influence of γ-irradiation and α-active aerosols in doses, exceeding the limiting permissible doses. In the first year of work in the presence of small total irradiation doses symptoms were detected which were characteristic for tuberculosis of the lungs (periodic subfebrile temperature, worsening of the general state, albuminuria and moderate hematuria, a non-acute pain syndrome). An active specific and general-restorative therapy was carried out with gradual liquidation of the urinary syndrome, but without pronounced improvement in the general state and sense of well-being. The conditions of the chest of the patient were improved, she was treated repeatedly and for a long time in hospitals, at health resorts, in the clinic.

The presence of general manifestations of asthenia, pains in the bones and joints and of insignificant deviations in the picture of the blood in the presence of clinical signs of recovery from tuberculosis of the kidneys was the basis for the fact that for the course of four to five years the disease was evaluated as chronic radiation disease. Only a recurrent outbreak of the tuberculous process with severe injury of the lungs (dissemination with breakdown, spitting of blood, the transition from a subfebrile temperature to a feverish state, and an acute acceleration in the erythrocyte sedimentation reaction), showed that, during all these years, the asthenization of the patient, as well as the other clinical shifts, were associated with the tuberculous process and could not be considered as resulting from the very brief contact with radiation.

A female engineer worked for the course of three years under conditions of insignificant exceeding of the limiting permissible levels of irradiation as regards the external γ-background and contamination with α- and β- active aerosols. Symptoms of disease arose in the course of a short period (two to three weeks at the time of pregnancy) and were characterized by the development of a typical diencephalohypertensive syndrome, accompanied by acute headaches, by rise in the /cerebrospinal/ fluid pressure, by characteristic vegetative-vascular crises with a rise in the temperature to 38°, polyuria, polydipsia. The pregnancy was spontaneously terminated on the seventh to the eighth week in the period when the patient was present in the hospital. After prolonged treatment, she was transferred to work under "clean" conditions.

The question of the etiology of the disease evoked great disputes; however, the presence of the length of professional service, the excretion of α-active substance with the feces and urine, the clinical syndrome of injury of the central vegetative apparatus in combination with the lability of the indexes of the peripheral blood inclined the physicians to the diagnosis of chronic radiation disease. Only subsequent observation of the course of the disease and the detection of gross organic symptoms typical of injury of the diencephalic region, as well as of significant disturbances in the function of the kidneys with an early eclamptic syndrome in the presence of repeated pregnancies facilitated the establishment of the correct diagnosis. From the very beginning, undoubtedly, there was a severe neuroinfection with injury of the region of the diencephalon, a stable organic defect of which (converging strabismus, changes in the reflex sphere) is retained in the presence of a significant restoration of the disturbed functions. Two subsequent pregnancies under conditions of the correct tactical approach with the necessary antieclamptic therapy ended in normal full-term births, and the patient has two healthy children at the present time.

In a locality characterized by a certain rise in the background activity of the medium, there was observed a certain quantity of cases of disease with typical changes in the blood, particularly in its myeloid part, in the nervous and digestive systems, with disturbances in the general state, of the dermal integuments. This disease had a similarity in symptoms with the syndromes which are observed in the presence of chronic radiation sickness. However, a very close familiarity with the patients, the conditions of their life, the medical history indicated a considerable dissemination in the given locality of cases of avitaminosis, associated with the disturbances of nutrition, brucellosis, dysentery. The

patients which had been registered, it turned out, were attacked by the harmful factors mentioned. The insignificant rise in the background /radiation/ renders the possibility of injury with radiation sickness extremely unconvincing.

Likewise in the presence of any other pathological picture, where the individual course of the disease reflects the combined action of several mutually influencing pathogenetic factors, the significance of each of them can be either insufficiently taken into account, or overestimated. Meanwhile, the sensitivity and reactivity of the organism in relation to each of them undoubtedly varies and the influence, for example, of infection, intoxication, or physical factors, etc., being accompanied by a lowering of the resistance and immunogenesis, can burden the course of another infection, intoxication, etc. The same thing also occurs with the influence of the radiation factor in the presence of the influence of other agents. One can indicate, for example, the course of dysentery in irradiated apes.

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