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SOME USSR RESULTS AND THEORIES PERTAINING TO ACUTE RADIATION SICKNESS

[Comment: The following report was published by P. D. Gorizontov, Corresponding Member Academy of Medical Sciences USSR, under the title "The Problem of the Pathogenesis of Acute Radiation Sickness" in Arkhiv Patologii, Vol 17, No 4, Oct-Dec 1955, pp 3-14. It reviews in some detail recent USSR work on the pathogenesis of radiation sickness and compares USSR results in this field with results obtained abroad.

Author's bibliography, figures, and tables mentioned in text are appended.]

One of the most urgent problems of contemporary medicine is that pertaining to radiation sickness. Under radiation sickness one understands the pathological condition brought about by the action of ionizing radiation.

It has been established that for the formation of a single pair of ions in the air an energy of no less than 32-35 electron volts is needed. The energy of visible light, infra-red rays, and ultraviolet rays has a magnitude of 2-10 electron volts. It follows that these types of radiant energy cannot as a rule bring about ionization. The ionizing types of radiant energy that are of the greatest significance for human pathology comprise gamma rays, X rays, alpha rays, beta rays, neutrons, and protons.

The energy of these types of radiation may approach millions of electron volts. We cannot in the present article discuss the characteristic properties of different types of ionizing radiation. We will only point out that the biological action produced by these types of radiation depends on the energy and consequently on the intensity of the processes of ionization. For that reason, notwithstanding the differences in the clinical syndromes of the pathological conditions produced by various types of radiant energy, one may speak of problems of the pathogenesis of radiation sickness which are common to all types of radiant energy. In the communications which have been published on the subject there is no unanimity concerning the essential nature of the radiation illness. Different theories in regard to the pathogenesis of radiation sickness have been advanced, particularly abroad.

For instance, an article by Jenkinson and Brown (1944) discusses nine theories which are used to explain the pathogenesis of radiation sickness, while an article by Shorvon mentions 16 such theories and a manual edited by Berens in 1952, seven theories.

From our point of view one of the basic shortcomings of the concepts which are adhered to at the present time is that in order to explain radiation sickness a major significance is ascribed to a single process and that on this basis attempts are being made to explain the complete pathogenesis of the condition involved. For instance, Jenkinson and Brown regard as the principal pathogenetic mechanism [which brings about the sickness] disturbances of the permeability of blood vessels. Warren and Whipple regard changes in the mucous membrane of the intestine and intestinal intoxication as the principal factor, while Ellinger advances the assumption that the role of histamine is of principal importance, with the result that some investigators who adhere to his view regard the pathogenesis of radiation sickness as similar to that occurring in shock.

A second error is that many investigators do not differentiate between the problem of pathogenesis and the problem of the biological effect produced by ionizing radiation.

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STAT

One cannot, of course, discuss the theories of pathogenesis without a knowledge of the action of ionizing radiation on biological substrates. However, one should not forget that the process of the development of a pathological condition is a more complex phenomenon, which is determined by the characteristics of the reactions of the organism depending on the development of its nervous system. In this context, we are of the opinion that in the complex problem of radiation sickness two special problems can be differentiated: (a) the mechanisms of the primary action of ionizing radiation on biological substrates in general, and (b) the mechanisms of the pathogenetic action of ionizing radiation, i. e., the problem of the harmful effect which is exerted on higher organisms.

These problems are interdependent and one may speak about their essential unity. However, this unity extends only to a certain point. As an example of failure to pay due attention to the qualitative peculiarities of the radiation affliction depending on the philogenetic and ontogenetic stage of development of the organisms affected, one may cite a review by Patt (1953), in which the mechanisms of defense against ionizing radiation are discussed without regard to the significance of the characteristics of differently constituted organisms.

The first problem, that of the action of ionizing radiation on biological substrates, is usually solved within the scope of general biological problems under the application of physicochemical and biochemical methods of investigation. At present the assumption in regard to the significant role played by processes of the ionization of the water is most generally recognized. To illustrate, an energy quantum of gamma radiation knocks an electron out of the molecule of water, so that a positively charged molecule of water is formed, while the electron combines with another molecule of water, forming a negatively charged molecule. In this manner an ion pair is formed:

$$H_2O - \bar{e} \longrightarrow H_2O^{+} \longrightarrow H^{+} HO$$

$$H_2O + \bar{e} \longrightarrow H_2O^{-} \longrightarrow H^{+} HO^{-}$$

In the presence of oxygen, different reactions arise which lead either to the formation of new components or as a result of recombination to the restoration of the initial substances:

$$H^{+} + \bar{e} \longrightarrow H$$

$$OH + OH \longrightarrow H_2\,O_2$$

$$H + H \longrightarrow H_2$$

$$H + O_2 \longrightarrow H\,O_2$$

$$OH + OH \longrightarrow H_2O + O, \text{ etc.}$$

In the process of the ionization of water, the greatest significance is ascribed to the following oxidizing radicals: atomic hydrogen (H) [sic], hydroxyl (OH), hydroperoxide (HO_2), and hydrogen peroxide (H_2O_2).

These radicals represent products of the decomposition of water arising under the effect of ionization. They exert an action on the protein molecules, particularly the most reactive structures of these molecules that contain sulfhydryl groups (-SH), and transform these groups into inactive sulfide groups (S-S).

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The oxidation of sulfhydryl groups of protein molecules can be represented in the following manner:

$$2\ SH + 2\ OH = -S - S - + 2\ H_2O$$

$$2\ SH + 2\ O_2H = -S - S - + 2\ H_2O$$

In this manner the functioning of the important cell enzyme systems which participate in the processes of synthesis is interfered with. This concept is based on assumptions made by Weiss and Barron.

It is in good agreement with the following facts: 1. The resistance to radiation increases as the water content of biological structures decreases (for instance, as a result of drying). 2. The susceptibility to injury decreases in connection with the reduction of the partial pressure of oxygen, because a reduction in the number of oxydizing radicals that are formed is brought about in this manner. 3. As is well known, the injurious action of ionizing radiation is independent of the concentration of biological structures in the solution (this constitutes the so-called dilution effect).

Since the aspects of the biological action of ionizing radiation are discussed more fully in a monograph by B. N. Tarusov, we will not go into details. However, one must point out that much remains unexplained as far as this problem is concerned. For instance, not a single author has demonstrated as yet in what manner the short-lived radicals mentioned above bring about the more remote effects involved in processes that take a long time. B. N. Tarusov's attempts to fill in this gap by advancing an assumption in regard to the role played by self-accelerating chemical reactions.

As far as the second problem is concerned, i.e., that of the mechanism of the development of the pathogenic condition, one may say that injury to cells or tissues under the action of ionizing radiation is regarded as the principal factor in the development of this condition. All theories of pathogenesis that are known to us are based on this assumption (i.e., the theories of A. S. Nikitin, Ellinger, Jenkinson and Brown, Cronkhite and Chapman, etc).

According to Nikitin, the scheme of the development of radiation sickness can be represented in the following manner:

Radiant energy → Damage to irradiated cells and their destruction (primary destruction of cells)

↓

Primary injury to protoplasm → Humoral reactions; Nervous reactions; General X- ray reaction

↓

Local disturbance of time regulation

↓

Disturbance of morphogenesis

↓

Suppression of growth and development

↓

Destruction of irradiated tissue (late reactions)

According to the concepts which have been outlined, the general reaction of the organism is brought about exclusively by action along the humoral route in the sense that various toxic and sensitizing substances enter the blood from the afflicted tissues.

STAT

In discussing the problem of the sensitivity of different tissues and cells to radiation on the basis of the injury produced, Holthousen (1920) regarded as sensitivity to radiation the dose of radiation which brings about degeneration of cells or necrobiosis. Using this criterion, some investigators arrived at the conclusion that as far as sensitivity to radiation is concerned, the blood cells are on top of the scale, while the tissue of the nervous system is the most resistant to radiation (Ellinger, Blum, de Coursey, et al).

As factors which determine the sensitivity of tissues to radiation, the following are pointed out with a certain measure of justification: (a) the mitotic activity of the cells, (b) the degree of differentiation, and (c) the intensity of metabolism. It has been established that the more intensely the processes of division (mitosis) proceed in the tissue, the less pronounced the degree of differentiation of the cells, and finally the more intensive the processes of metabolism which take place in the tissue, the higher the sensitivity of the tissue to ionizing radiation is found to be.

Gimpel'man, Lisko, and Gofman in their monograph point out that there are two possibilities of injury to the cells: injury to dividing cells and injury to dormant cells.

In an experiment with a culture of chicken fibroblasts it has been shown that in order to bring about degeneration of dormant cells, the application of 2,500 roentgen is necessary, while dividing cells perish when a dose of 100 roentgen has been applied. The dormant cells do not undergo any modifications after application of the dose of radiation which has been mentioned until they begin to divide. Then the cell either perishes or produces two daughter cells incapable of surviving.

On the basis of the concepts outlined above, Cronkhite and Chapman suggest that the pathogenic condition develops as follows. Having a greater resistance to radiation, the mature cells of the organism that has been irradiated do not perish, while the young propagating cells are affected.

As a result, in view of the fact that the natural death of mature cells is not compensated by the generation of new cells, devastation of a system (e.g., blood system) of the organism which is affected takes place and this system is finally put out of commission. In regard to the ideas which have been outlined, one may say that there is no reason for denying that a direct injurious effect is exerted on the cells and tissues as a consequence of exposure to ionizing radiation. Furthermore, the sensitivity of different tissues of the organism being irradiated is actually different.

However, we regard it as entirely wrong to ascribe the sensitivity of cells to the structural damage inflicted on them because we do not have at our disposal as yet morphological methods which make it possible to evaluate with certainty the functional condition of cells, for instance, of cells of the nervous system. It is precisely this circumstance which led to the faulty conclusion in regard to the insensitivity of nerve cells to the action of ionizing radiation. The work done by USSR scientists Tarkhanov, Zhukovskiy, Nenenov, Kupalov, Bakin, Livanov, and others has demonstrated that the functions of the central nervous system are disturbed as a result of the action of ionizing radiation.

In a paper presented at the Ninth Session of the Academy of Medical Sciences USSR we described the results of investigation of the higher nervous activity of rats, of the spinal reflexes of dogs, and of electroencephalographic measurements carried out on rabbits.

STAT

The investigations of the cortical activity of irradiated rats have shown that in the process of the development of acute radiation sickness, acute disturbances of the conditioned reflex activities take place (A. Grafov). After an initial strong reinforcement of conditioned reflexes, a sharp weakening of conditioned reflex activity develops. Finally, a third period can be differentiated, that of recovery and relative normalization. This period is characterized by the persistent instability of the processes of stimulation and inhibition. The length of the individual periods or stages and the time at which they begin depend on the magnitude of the dose of radiation which has been applied and the typological characteristics of the organism affected.

The same periodicity of changes in the cortical activity was established prior to that by M. N. Livanov on rabbits with the use of electroencephalographic methods of investigation.

These changes are apparently expressed, first of all, in a disturbance of internal inhibition, because we established on rats that a breakdown of conditioned inhibition takes place several minutes after irradiation and is associated with a stoppage of differential inhibition accompanied by disturbances of extinction.

All these changes are subject to the same regularities which are characteristic for acute pathological processes of diverse etiology. For instance disturbances of internal inhibition were observed after application of anesthetics, intoxications, and infections (A. A. Lindberg, V. K. Federov, A. G. Ivanov-Smolenskiy, and others). We discussed this subject in another article.

Clinical observations have shown that changes in the nervous system ensue very promptly, i.e., several minutes after the beginning of the application of therapeutic doses of radiation (Grigor'yev). In other words, these changes occur at a time when there is no reason to assume that injury to cells has taken place. In this context, we cannot exclude the possibility that tissues are injured by reason of disturbances of the normal reflex regulation.

The possibility that there is an indirect injurious effect on tissues produced by ionizing radiation through the medium of the system midbrain-hypophysis-suprarenals was shown in experimental investigations by Langendorf and Lorenz (1952) in their work on the causes of lymphopenia which develops after irradiation. In the experiments by the investigators mentioned, approximately the same degrees of lymphopenia were obtained upon local irradiation of the hip, the testicle, and the hypophysis. Furthermore, the same lymphopenia originated without any exposure to radiation under unfavorable conditions, for instance, when the rat was held motionless on the operating table for several minutes. In all these experiments the lymphopenia could be eliminated by prior adrenalectomy. These facts testify to the circumstance that one cannot regard the lymphopenia of the irradiated animals only from the standpoint of a specific sensitivity of lymphocytes to ionizing radiation and of a direct action of radiant energy on lymphocytes.

Similarly, one cannot regard the devastation of blood-forming elements which follows irradiation solely as a result of direct injury inflicted on the young reproductive cells of the organs of hemopoiesis. Booz, Betz, and Firket (1954) have shown that upon general irradiation of guinea pigs with doses ranging from 700 to 8,000 roentgen, i.e., doses which exceed by several times the quantities of radiation producing a lethal effect, the tissue of the spleen of the experimental animals will not lose its capacity to regenerate if it is transplanted within a day into the healthy, nonirradiated body of another guinea pig.

STAT

If a leg of a rabbit is exposed to doses amounting to 3,000-5,000 roentgen and the body of the rabbit and its other legs are protected from the direct action of the ionizing radiation, one finds that at the expiration of approximately 3 weeks an ulcer develops on the leg which has been exposed to radiation. Approximately the same kind of ulcer develops within about the same time in a symmetrical section of a leg that has not been irradiated (M. M. Livanov). The possibility that there may be a reflected action of ionizing radiation has usually been explained by humoral effects. For instance, P. V. Sipovskiy, in studying the histology of the bone marrow, found subsequently to irradiation changes in spots which had not been irradiated. In reference to this, he states that in order to explain the reflected action of X rays, one must assume that this action is the result of a secondary effect exerted by products of protein decomposition (for instance, the products resulting from the death of cell elements). These products of the decay of cells penetrate into the blood and subsequently bring about a number of changes in other organs.

It is difficult to explain from this point of view why the ulcer on the leg which has not been irradiated develops simultaneously and originates in a symmetrically disposed location.

The ways in which the pathological process is brought about after irradiation is more complex; they cannot be ascribed solely to a direct injury and to the action of substances that originate in the injured tissues. The changes in the nervous system, the occurrence of which has been established principally by USSR scientists, and the facts cited above testify to the possibility that reactions may develop which are transmitted through the nervous system and the system of neuro-endocrinic glands (the hypophysis and the suprarenals).

In this context, the problem in regard to the initial ways of the process and of the location where the principal injury of the nervous system takes place remains unsolved. One cannot, of course, assume that the nervous system is affected everywhere in the same measure by some sort of a diffuse process or that all pathological conditions are the result of a primary disturbance of cortical activity. In an investigation dealing with the problem of the application of I. P. Pavlov's teaching to the problems of pathophysiology, we pointed out that it is necessary to determine in every disease the principal links which are affected when a disturbance in the functioning of the nervous system takes place.

The results of experimental investigations in which simians were irradiated lead to the conclusion that affliction to a predominant extent of the higher vegetative centers must be assumed (Clement and Holst). Experiments which we have carried out on dogs testify to disturbances of the temperature regulation in irradiated animals. This phenomenon may be an expression of the fact that the activity of the corresponding part of the vegetative system has been affected. However, the problem in regard to the initial stages and to the location of the maximum injury to the nervous system cannot be regarded as solved as far as the role of these effects in the pathology of radiation injury is concerned.

In trying to clarify the role of the nervous system in the mechanisms of the pathogenetic action of ionizing radiation, we do not exclude the possibility that the humoral factor may participate in the pathogenesis.

Notwithstanding the fact that much attention has been paid in the radiobiological literature to the problem of toxemia, this problem has not been solved in a unanimous fashion. The most convincing data were obtained in experiments carried out on parabiotic animals in which the blood circulation systems were merged by establishing a mutual connection between the skin and the

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STAT

muscles. This connection was brought about by sewing together two animals and allowing the tissues to heal. Rats or guinea pigs of the same litter and the same size were commonly used in these experiments. Under these conditions the irradiation of one of the animals brings about leukopenia in the other animal, which has not been irradiated. By using this method, Edwards and Summers did not obtain any necrobiotic changes in the organs of the animal that had not been irradiated. On the basis of this result, they deny the possibility of the formation of a toxemic component in the pathogenesis of radiation sickness. These authors are inclined to explain the leukopenia by a simple mingling of the blood.

However, Kolpakov and Khodos, who carried out experiments on parabiotic rats, deny this possibility, because in one of the variants of the experiment they separated the parabionts within several minutes after irradiation, i.e., at the time when the irradiated animals were in the stage of leukocytosis which, as is known, precedes the development of leukopenia. Under these conditions one cannot explain by mingling of the blood the leukopenia which develops subsequently in the animal that has not been irradiated.

Experiments of this type were also carried out in the USSR on dogs. By using the method of merging the blood streams, the effects on a healthy dog of the blood from an irradiated animal and a nonirradiated animal were investigated. Usually about 50% of the circulating blood was replaced when the method of merging the blood streams was used. Of course, we did not expect that radiation sickness will develop under the effect of the blood of an irradiated animal and regard this formulation of the problem as faulty. By using the method of merged blood streams, one can only detect the accompanying role of the humoral factor in the development of some aspects of radiation sickness.

Experiments with the use of the method of merged blood streams have actually shown that the blood of irradiated animals brings about leukopenia (V. D. Rogozhin).

One must note that under the experimental conditions in question the nonirradiated recipient of the blood develops not only changes in the composition of the peripheral blood but also modifications of hemopoiesis in the bone marrow. When punctates of the bone marrow of the nonirradiated recipients were taken in cases when the donor was an irradiated animal, it could be established that changes in the cell composition of the bone marrow had taken place. Although these changes were less sharply pronounced, they were analogous to those observed in animals which suffer from radiation sickness (N. K. Yevseyeva).

Normally, the number of myeloid elements of the bone marrow is higher than the quantity of erythroblastic elements. For that reason the ratio of erythroblastic cells to myeloid cells is always less than unity. This ratio in dogs is most often within the range 0.3-0.6.

According to the experimental results, this ratio in healthy dogs remains within normal limits after merging of the blood streams. When a mutual blood exchange between a healthy dog and an irradiated dog has been carried out, this ratio changes in a healthy animal in the same direction as in an irradiated animal.

It has been established that upon irradiation with a dose of 500 roentgen, unless complete devastation of the bone marrow takes place, the content of erythroblastic and myeloid elements changes in such a manner that the relative quantity of erythroblastic cells increases. As a result of this the ratio increases up to unity and may become higher than unity. The same increase of the ratio, although less pronounced, takes place in dogs which have received blood from an irradiated animal in the course of an exchange transfusion. The dynamics of the modifications of the ratio in three dogs are shown in Table 1.

STAT

Still more convincing were the data obtained by including in the system of merged circulation individual parts of the body of irradiated animals (G. P. Gruzdev). By joining the circulation of various tissues of the head, extremities, intestine, and spleen of irradiated animals to the general circulation of nonirradiated animals, the physiological indexes (blood pressure and respiration) and the composition of the blood of the nonirradiated animal serving as recipients were modified. The changes produced in this manner were then studied.

As a result of the experiments which have been carried out, it was established that blood which has pronounced hypotensive properties flows from the head of an irradiated animal while blood flowing from a leg has the property of producing sharply expressed and persistent leukopenia, or more correctly neutropenia. A lymphopenic effect was produced by the blood flowing from the spleen. Effects of this type have never been found to result from the blood of the same organs of nonirradiated animals. Figure 1 [not reproduced in this report; see page 9 of the source] represents a kymogram of changes in the blood pressure produced by blood flowing from the head of an irradiated dog. In Figure 2, curves are given which describe the changes in the number of leukocytes produced by blood derived from the leg of an irradiated animal (the dose of total irradiation of the dog amounted to 800 roentgen).

At present we have the task of determining the nature of the active substances found in the blood and of studying the dynamics of their development, because our experiments were carried out as late as the 3d day after irradiation.

The literature contains a great number of communications dealing with the role of histamine in the development of radiation sickness. However, data on the manner in which the histamine content changes in the blood of large laboratory animals were not available.

For that reason, T. M. Mel'gunova investigated the problem by carrying out experiments on irradiated dogs. This investigator, by using basically the determination of histamine-like substances on the atrophinized cat as an experimental method, showed that as the development of the radiation sickness advances, the number of dogs which contain histamine-like substances in the blood increases; the maximum is observed on the fifth day of the disease (see Table 2).

The data cited cannot be regarded as proof of the decisive role of histamine, particularly during the initial periods of the development of the sickness. However, they demonstrate that histamine-like substances are actually formed in the irradiated body when the effect produced by the radiation is intense (i.e., when a dose of 600 roentgen has been applied).

On the basis of the results discussed above, we may draw up a scheme of the routes along which the pathogenetic action of ionizing radiation is exerted. This scheme, in addition to comprising the direct injurious effect on tissues, includes routes which are activated through the medium of the nervous system and also humoral routes along which the pathogenetic action is exerted (see Figure 3). In the scheme represented in Figure 3, the routes along which normalization and restoration of the disturbed equilibrium take place are also shown. These routes proceed along the nervous system.

Pavlov's teaching extends the possibilities of understanding the pathogenetic effect of etiological factors. Specifically, in the pathology of radiation, concepts based on Pavlov's teaching make it possible to interpret with facility the otherwise inexplicable circumstance that there is no correspondence between the amount of energy absorbed and the biological effect produced. Calculations show that upon general irradiation of the organism acute pathological

STAT

changes are produced by doses which are many times smaller than those necessary for inflicting injury on the cells. In order that visible changes in cells may be observed, one must subject to radiochemical action 1/10 - 1/100 of the total number of molecules of the cell protoplasm (Dessauer). When a living organism has been irradiated with 1,000 roentgen, injury to cells is produced, notwithstanding the fact that radiochemical changes take place approximately in only one out of 100,000,000 molecules of cell protoplasm. This figure is obtained if the calculation is carried out on the basis of direct action of ionizing radiation on the cells (Gampel'man, Lisko, Gofman, and Zirkle).

This significant discrepancy in the biological effect is explained by the fact that in the total organism the action of ionizing radiation may be exerted not only as a nociceptive irritation, i.e., an irritation which directly brings about injury of the tissues, but also is an irritation which produces excitation of nerve elements of the body.

This postulate is of fundamental significance, inasmuch as the energy levels at which the irritations indicated above exert their effect are entirely different: the level is much lower in cases when the environment exerts its effect through the nervous system of the organism. This is the reason why calculations based on data pertaining to models representing the simplest organisms or to isolated tissues are not always applicable when the effects on complex and highly developed organisms are considered.

If one envisages the possibility that pathological processes take place as a result of disturbances of the regulatory function exerted by the nervous system, the dependence of general symptoms not only on the dose of absorbed energy, but also on the magnitude of the area which has been irradiated becomes understandable. For instance, although local irradiation of rather extensive surfaces (i.e., the whole head or the surface of the abdomen) can be carried out [without a lethal effect] by means of doses of the order of 1,000 or more roentgen, the death of a dog may ensue subsequently to general irradiation with a dose of only 300 roentgen or even less. It seems to us that this difference depends on the number of afferent systems which have been involved in the action of ionizing radiation. From this point of view, it becomes clear why irradiation of the abdomen (a section which is particularly rich in sensory elements) brings about most readily general changes in the organism that are typical of radiation sickness.

Thus, in discussing the pathogenetic action of ionizing radiation, one must consider not only its role as a factor which directly injures tissues, but also the part played by it as an irritant which exerts an effect on the nervous system. Irritation of the peripheral afferent systems in irradiation actually takes place, as M. N. Livanov's investigations have demonstrated. After irradiation there is a disturbance of normal impulse formation ["impulsation"] and development of spontaneous biological currents in peripheral cutaneous nerves.

However, the understanding of the problem of the pathogenesis of radiation sickness is not complete if only the mechanisms mentioned above are considered. At the height of the pathological condition, other etiological factors become active and may involve autoinfection of the organism as one of the contributing effects (P. N. Kiselev).

Disturbances of permeability which arise under the effect of ionizing radiation may turn out to be the decisive factor responsible for the penetration of bacteria into the tissues of the organism from places which they constantly inhabit (for instance, the intestine). These so-called "exit bacteria," on penetrating into the tissues, may produce phenomena of autosensitization. It follows from work by Sanarelli, Shvartsman, and particularly P. F. Zdrodovskiy

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that hyperergic inflammation processes may arise which are characteristic for the development of so-called anaphylactoid reactions. The sensitization of tissues which is necessary for the occurrence of these reactions develops within several hours. Under these conditions the introduction into the blood stream of products derived from bacterial bodies leads to acute hemorrhages. The increased permeability of the intestinal walls of irradiated animals was demonstrated in experiments carried out by P. N. Kiselev in which foreign serum, thorotrast, or bacteriophage had been introduced. Modification of the permeability of blood vessels was noted by D. N. Mogil'nitskiy and his collaborators. The dynamics of changes in the permeability and strength of the walls of blood vessels during the development of acute radiation sickness were studied in the USSR by V. A. Razorenova on different species of animals. M. V. Gradova, using A. D. Ado's method, demonstrated in our laboratory the possibility of increased accumulation of antigens in the tissues of the irradiated body.

Without considering the special problem in regard to increased permeability, we will only point out that this process is of great significance for sensitization and for the development of a modified reactivity of the irradiated organism.

The ways along which sensitization may take place are shown in Figure 4, which depicts the second stage, or according to our terminology the polyetiological stage, of the development of radiation sickness. The fact that sensitization of an irradiated organism by bacterial cells and the products of their decay takes place has been pointed out long ago by A. Yugenburg, L. G. Perets, and R. S. Mostova. They also pointed out the role which the effects that have been mentioned play in the development of the decisive reaction.

Subsequently, the increased permeability of the vascular endothelium leads to a development of bacteriemia and of septic conditions. All of these processes develop and their occurrence is not difficult to understand, if the sharp lowering of the phagocytic activity of the elements of connective tissue is taken into consideration and it is realized that this phenomenon is accompanied by a thorough-going leukopenia and a sharply lowered capacity to form antibodies as well as changes in the activity of these antibodies.

The possibility that the irradiated organism may become infected has been established by many investigators and cannot be doubted. Much remains to be done before the pathogenesis of radiation sickness can be completely understood. Future investigations will show which processes play a decisive role in different stages of the sickness.

Conclusions

Within the scope of the complex problem involved in the pathogenetic action of ionizing radiation, one must distinguish between (a) the mechanisms of primary action on biological substrates, i.e., cells and tissues, and (b) the more complex mechanisms of pathological conditions affecting higher organisms that develop on the basis of the primary effect.

As far as the action of ionizing radiation on biological substrates is concerned, the most generally accepted theory is one which regards the observed changes from the standpoint of the assumption that water is ionized and oxidizing radicals develop as a result of the action of radiation.

To understand the pathogenetic action of ionizing radiation, we cannot limit ourselves to a consideration of the direct action of ionizing radiation on the tissues of the organism. It is possible that other effects are exerted through the medium of the nervous system. This assumption is supported by numerous facts which testify to the occurrence of changes in the functioning of various divisions of the nervous system.

STAT

The problem in regard to the initial stages of the development of the pathogenic process and to the localization of the predominant affliction of the nervous system in the course of radiation sickness remains unsolved.

The toxemic factor undoubtedly plays a role in the development of the radiation affliction. At present one may regard as established that substances which exert a hypotensive effect appear in the blood of the irradiated organism and bring about changes in the cell composition of the blood.

Different tissues play different roles in contributing to changes of biological functions produced in the organism under the effect of radiation. By merging the blood streams of two animals it could be shown that the head of an irradiated animal (dog) evolves substances which have a hypotensive activity while the organs of hemopoiesis evolve substances the principal activity of which leads to changes in the composition of the blood.

Histamine-like substances appear in the blood of irradiated animals. The maximum of the development of these substances takes place on the 5th day after irradiation.

The processes of autoinfection and autosensitization play a considerable role in the development of acute radiation sickness.

The routes along which the pathogenetic activity of ionizing radiation is exerted have been schematically outlined on the basis of published data and experimental results.

[Figures are appended.]

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Table 1. Changes in the Ratio of Erythroblastic To Myeloid Elements in Dogs

	Action to Which Animal Has Been Subjected	Index Showing Ratio of Erythroblastic to Myeloid Elements in Dogs Subjected to Action Indicated in Column 2										
		Prior to Experiment	Time in Days									
			1	3	5	7	10	12	15	20	30	45
1st dog	Irradiation with 500 r	0.4	0.4	0.55	0.62	0.3	1.9	2.5	--	--	1.8	0.8
2d dog	Exchange transfusion with an irradiated dog serving as the donor	0.4	0.89	0.77*		0.71	0.67	1.06	--	0.56	0.47	--
3d dog	Exchange transfusion with a nonirradiated dog serving as the donor	0.4	0.3	0.52	0.46	0.48	0.29	0.37	0.54	0.5	0.31	--

* On the 4th day

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Table 2. The Development of Histamine-Like Substances in the Blood of Irradiated Dogs

	Total Number of Dogs Subjected to Investigation	Number of Dogs Exhibiting Activity of the Histamine Type in the Blood		Time Since Exposure to Radiation
		In absolute figures	In %	
Nonirradiated animals	44	3	6	
Irradiated animals	27	12	44	Within the first few hours
	15	5	30	1 day
	43	31	72	5 days
	30	6	20	7 days
	31	6	20	10 days
	41	8	20	Periods in excess of 10 days

FIGURES

[Figure 1 of source not reproduced here.]

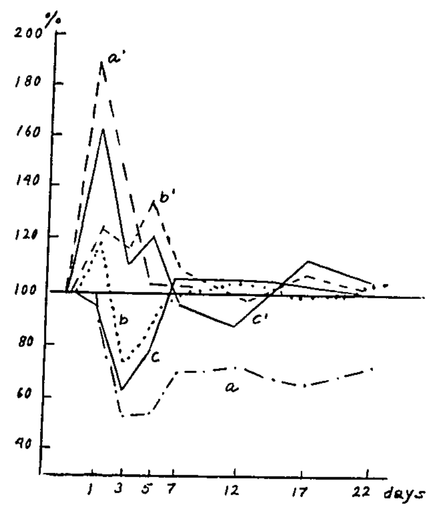
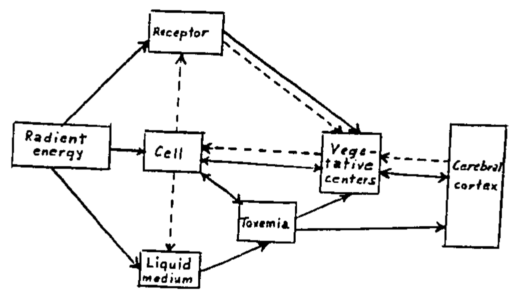


Fig 2. Changes in the Number of Leukocytes (in Percent of the Initial Quantity) in Recipient Dogs Which Received Blood From the Leg of a Healthy Dog (Controls a', b', and c') or From the Leg of Irradiated Dog (Experiments a, b, and c)



—— Routes along which injury takes place
- - - Routes along which adaptation develops

Fig 3. Scheme Showing Routes Along Which the Pathogenetic Action of Radiant Energy Is Exerted

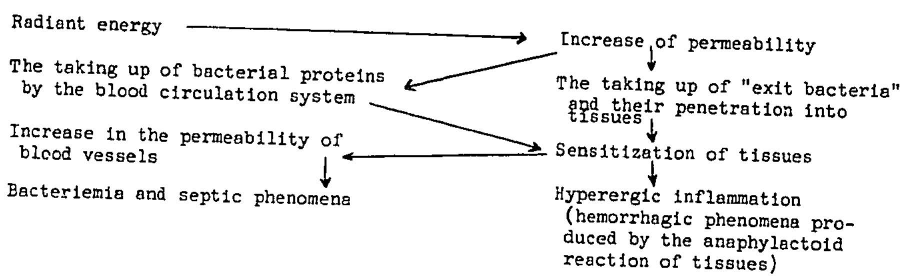


Fig 4. Scheme That Describes the Second (Polyetiological) Stage of the Development of Radiation Sickness

* * *

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