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FOREWORD

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TRANSLATIONS FROM MEDITSINSKAYA RADIOLOGIYA

- USSR -

[Following is the translation of three articles in the Russian-language periodical Meditsinskaya Radiologiya (Medical Radiology), Vol 7, No 8, Moscow, August 1962. Additional bibliographic information accompanies each article.]

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CELL IMMUNITY CHANGES DURING CHRONIC,
SUSTAINED IONIZING RADIATION

- USSR -

[Following is a translation of an article by P. N. Kiselev and P. A. Buzini in the Russian-language periodical Meditsinskaya Radiologiya (Medical Radiology), Vol 7, No 8, Moscow, August 1962, pages 59-65.]

At the present time there has been a great deal of study on the disturbance of natural and acquired immunity in acute radiation sickness. There are, however, only isolated investigations of the effect of chronic ionizing radiation on mechanisms of immunity (P. N. Kiselev and P. A. Buzini; V. N. Sivertseva; O. G. Alekseyeva).

Five years ago our laboratory began experimental investigations on the study of chronic, sustained action of γ -irradiation Co^{60} on infection and immunity. In the data published during this time, we examined investigation results of the effect of sustained action of ionizing radiation on humoral immunity and the course of certain processes of infection (P. N. Kiselev and P. A. Buzini; P. A. Buzini; V. N. Sivertseva). In order to have a clear picture of the disturbance of natural immunity and immunogenesis in these conditions, however, it is necessary to clarify the effect of sustained small dosage radiation cell immunity and compare observed disturbances of the humoral immunity with changes in immunity mechanisms of the cell. It is only under these conditions that we can understand not only the character and completeness of the disturbances, but also their significance.

In previous research it was ascertained that during the chronic sustained action of ionizing radiation on the organism changes in the humoral immunity occur. This is expressed in a decrease of bactericidal capacity of the blood, and increase in sensitivity to infection of the irradiated organism, and in the final analysis the development of auto-infectious processes. It was found that the greatest disturbance of natural immunity was observed in the case where the organism was subjected to radiation in the period of embryogenesis. Immunity disturbance passes through a stage of humoral immunity activation and the process

of immunogenesis. This phenomenon is evidence that during the process of chronic irradiation of the organism, in response to irradiation injury, protective immunizing mechanisms begin to function. With the exhaustion of adaptive mechanisms, there is an onset of humoral immunity decrease. The data obtained has shed a certain amount of light on the character and course of changes in humoral immunity.

The present article examines experimental data on the study of the influence of chronic, sustained γ -irradiation Co^{60} on cellular immunity. Experiments were performed on rabbits, guinea pigs, white mice and rats. The same irradiation techniques were used as before (P. N. Kiselev and P. A. Buzini). Dosage strength varied within limits of 0.5-4.3 g/day; total dosages 50-4,000 g. The animals were observed for a period of five years.

Table 1

Total irradiation dosage, r	% active in segmented and polymolecular monocyte phagocytosis	Phagocytic count	Phagocytic character in			% detail	P
			%				
			complete	mixed	complete		
465	78	9.8	60	24	18	0	4.1
700	67	4.3	20	27	53	14.3	4.6
1 000	49	1.3	12	19	69	70.1	5.1
1 150	37	0.6	6	11	83	89.9	3.6
Контроль	63	10.3	62	28	10	0	3.6

Changes in the activity of phagocytic leukocytes during chronic, sustained irradiation of guinea pigs Co^{60} in relation to total dosage (dosage strength 3.5 g per day)

We studied the results of chronic, sustained ionizing irradiation as it affected the phagocytic capacity of leukocytes, the segregational function of the reticulo-endothelial system, and the sensitivity of somatic cells to toxins and viruses. We studied the phagocytic activity of leukocytes on guinea pigs according to the technique of V. M. Berman and E. M. Slavskaya. We studied the absorbing and digesting capacity of leukocytes in relation to *Bact. typhi abdominalis*. Table 1 presents data on quantitative and qualitative changes in the phagocytic activity of leukocytes in guinea pigs during irradiation.

We see from Table 1 that the total irradiation dosage of 465 r was not lethal for guinea pigs and led to comparatively minor changes in the phagocytic activity of leukocytes. With increase in time intervals that the animals spend in the sphere of ionizing irradiation, and the increase in the general total dosage, eventual weakening of the phagocytic activity of leukocytes occurs. Phagocytic weakening parallels

the growth of percentage of detail and affects not only the absorbing, but also the digestive, capacity of leukocytes. At total dosages of 700-1,000 g, however, the absorbing capacity of leukocytes was disturbed to a smaller degree, and the digestive capacity to a larger degree. In subsequent significant increase of total dosage of irradiation, there was less expression of a proportional relation between the phagocytic count and the phagocytic character.

After establishing this general pattern for the disturbance of the phagocytic capacity of leukocytes under chronic, sustained irradiation, we studied phagocytic changes in relation to the age of irradiated animals. We had two objectives in our work. First we investigated changes in the phagocytic capacity of leukocytes in the offspring of animals who were pregnant during the course of irradiation. We also studied disturbances of the phagocytic function of the leukocytes of mice whose course of irradiation was initiated at various periods in the post-natal development. The aim of all this experimentation was to clarify which of the ontogenetic periods (starting with embryogenesis and continuing through sexual maturity) is the most vulnerable in the immunological sense under chronic irradiation.

The investigation of phagocytic activity of leukocytes under irradiation in mice during the period of embryogenesis was conducted on two groups of animals. The first group — mice, born of parents irradiated during the period of intra-uterine development (780 r dose) and post-natal development (200 r dose). The second group was composed of the same mice, which were removed from the sphere of radiation immediately following birth. The control group consisted of mice weighing 10-12 g which were not subjected to irradiation, and which were born of non-irradiated parents. Animal phagocytosis was investigated according to the attainment by experimental animals of the weight of the mice from the control group (10-12 g).

The results of the experiments are presented in Table 2.

As we see from Table 2, irradiation during the period of embryogenesis leads to functionally non-full-valued, in the phagocytic sense, leukocytes even under relatively small total dosage (200 r). The immediate removal of mice, following birth, from the sphere of ionizing radiation does weaken the eventual injury of this defensive function of the organism, yet phagocytosis in experimental animals is significantly weaker than in the control group. Consequently these experiments indicate a significant sensitivity of the leukocyte phagocytic function under irradiation of the organism in the period of intra-uterine development.

Table 2. Changes in phagocytic activity of leukocytes in mice subjected to chronic irradiation during the period of intra-uterine development at dosage strengths of 4.3 r/day (experiments in vitro).

Группа	1) % клеток, участвующих в фагоцитозе	2) Фагоциты в поле зрения	Характер фагоцитоза		
			3) Фагоциты в поле зрения	4) %	5) %
			6) завершённый	7) смешанный	8) незавершённый
5) Мыши, облучавшиеся в период эмбриогенеза и после рождения (суммарная доза 200 г)	51	3,2	11	26	63
9) Мыши, облучавшиеся в период эмбриогенеза и удалённые из сферы радиации после рождения	69	6,8	39	31	30
10) Контрольные мыши	80	9,1	59	33	8

- Legends:
- (1) Group
 - (2) % of cells participating in phagocytosis
 - (3) Phagocytic number
 - (4) Character of phagocytosis
 - (5) Complete
 - (6) Mixed
 - (7) Incomplete
 - (8) Mice irradiated during the period of embryogenesis and following birth (total dosage, 200 r)
 - (9) Mice irradiated during the period of embryogenesis and removed from the sphere of radiation following birth
 - (10) Control mice

In another series, investigators studied changes in phagocytic activity of leukocytes in relation to age. With this aim, mice were irradiated following birth at the ages of 3½-5, 6-7 weeks and at the attainment of a 16-18 g weight. Irradiation was performed at dosages of 1.29 r/day and prolonged for 14 months. Phagocytosis was investi-

gated after a total dose of 520 r. Investigation results showed that, at the same irradiation dosage, the disturbance in phagocytic activity was unequal in animals irradiated at various ages (Table 3).

Table 3. Changes in phagocytic activity of leukocytes in relation to the typhus bacillus in mice irradiated at different ages (dosage strength 1.29 r/day, dosage 520 r)

(1) Группа	(2) Количество животных	(3) % лейкоц. участвующих в фагоцитозе	(4) Фагоцитическое число	(5) Характер фагоцитоза (6)		
				(6) завер- шенный	(7) неза- вер- шенный	(8) сме- шанный
%						
(A) Подопытные						
(9) Мыши, облучавшиеся в возрасте 3½-5 недель	20	59	6,7	6	69	25
(10) Мыши, облучавшиеся в возрасте 6-7 недель	20	73	8,3	24	57	19
(11) Половозрелые (16-18 г)	20	80	8,6	53	66	11
(B) Контрольные						
(12) 3,5-5 недель	20	81	8,9	56	34	10
(13) 6-7	20	80	9,1	62	30	8
(14) Половозрелые	20	78	8,8	57	34	9

- Legends:
- (1) Group
 - (2) Number of animals
 - (3) % of cells participating in phagocytosis
 - (4) Phagocytic number
 - (5) Phagocytic character
 - (6) Complete
 - (7) Incomplete
 - (8) Mixed
 - (9) Mice irradiated at ages of 3½-5 weeks
 - (10) Mice irradiated at ages of 6-7 weeks
 - (11) Sexually mature (16-18 g)
 - (12) 3.5-5 weeks
 - (13) 6-7
 - (14) Sexually mature
 - (15) Experimental
 - (16) Control

In the experiments, we not only noted a disturbance in phagocytic activity of leukocytes in animals subjected to chronic irradiation, but also discovered a relation with the period of the development of the organism when it comes into the sphere of radiation.

At the same time that the phagocytic activity of leukocytes was

studied, we also investigated the segregational function of the reticulo-endothelial system through marked S^{35} B. coli and colloidal Au^{198} . We conducted experiments on white mice who had received varying total dosages of irradiation, injecting them intravenously with either marked bacteria or Au^{198} . We evaluated the function of the reticulo-endothelial system according to the technique of Benacerraf, Halpern et al. Figure 1 presents data concerning the function of the reticulo-endothelial system, derived on the basis of studying how the blood purifies itself from marked S^{35} B. coli after the action of 100-1,650 r at the same dosage strength (2.4 r/day). As we see from Figure 1, at total dosage of 100-550r, one can observe some stimulation of the function of the reticul-endothelial system, expressed by an increase in the rapidity of the blood cleansing process from foreign particles. The stimulation that occurs is preceded by a stage of stable weakening of the segregational function of the reticul-endothelium. However, even at total doses of 1,650 r, which was fatal in 85% of our cases over a two-year period, we did not observe complete blockage of the segregational function of the reticulo-endothelial system. This indicates great restorative capacity under chronic irradiation. Consequently, chronic, continuous action of relatively small doses of ionizing radiation finally leads to weakening of the function of the reticulo-endothelial system, although the eventual weakening passes through a stage of stimulation of its segregational function. The organism's immunity depends in a certain measure on the degree of somatic cell sensitivity to various pathogenic agents, including bacterial toxins and viruses. We therefore evaluated cell immunity of chronically irradiated animals both according to changes in their sensitivity to endo- and exo-toxins of various bacteria, and according to their response reaction to the virus as an intracellular parasite. In this connection we investigated somatic cell reaction to virus induction of grippe, and by this we judged the changes in their defensive function. This would be analogous to judging the defensive function in general according to paranecrosis or cell ability to form vital stain granules (D. N. Nasonov and V. Ya. Aleksandrov).

Figure 1. Blood purification from Bact. coli, marked S³⁵, under chronic, continuous Co⁶⁰ irradiation of the organism in relation to dosage magnitude (dosage strength, 2,419 r/day)

$$K = \frac{\log C_1 - \log C_r}{t}$$

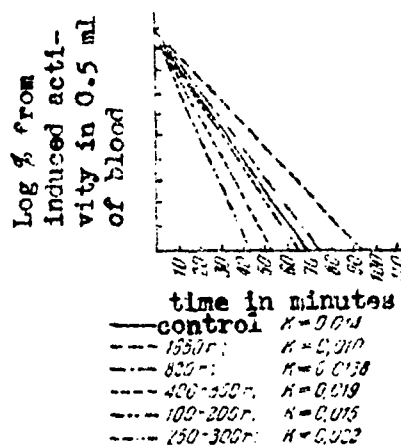


Table 4. Dynamics of the formation of defensive, oxyphilic components in the cells of the trachea and main bronchi of mice under chronic irradiation (dosage strength: 1.29 r/day) when infected with weakly pathogenic strains of grippe virus, type A.

Total dosage, r	(1) Среднее количество включений на 900 эпителиальных клеток				
	24 hours	36 hrs.	48 hours	72 hours	5 days
220	320	415	150	4	0
430	51	64	128	78	30
control	230	315	315	13	0

Legend: (1) Average quantity of components for 900 epithelial cells

The research of Harford and Hamlin, and V. E. Pigarevskiy shows that, in response to the induction of weakly pathogenic grippe virus into tracheal epithelium, basophilic and oxyphilic components appear in cell cytoplasm. The basophilic components consist of accumulations of virus particles, while oxyphilic formations reflect the cell's defensive reaction. A. A. Smorodintsev established that there is a disturbance of the formation of oxyphilic components in cells during acute radial injury to the organism. As a result of these concepts, we infected irradiated mice (1.29 r/day, after total doses of 220 and 430 r) as well as control mice with grippe virus A, and did not approach them again for 1-5 days. We investigated the epithelium of the trachea and main bronchi histologically for the presence of defensive oxyphilic components according to the Dominici-Pigarevskiy method. We present the results of this research in Table 4.

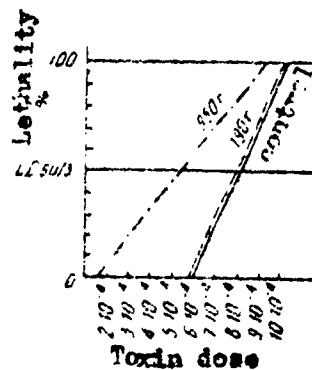
As we see from Table 4, chronic action of relatively small irradiation doses on white mice leads to a change in the dynamics of the formation of defensive oxyphilic bodies in epithelial cells of the trachea and main bronchi, in response to cellular penetration of weakly pathogenic strains of grippe virus. At total radiation dosage of 220 r, we can observe stimulation of the formation process of defensive components and some increase in the tempo of their disappearance from the cytoplasm; this indicates an increase in the defensive reaction. Increase of total dosage to 430 r, on the contrary, leads to a significant expression of a decrease in the formation of oxyphilic cellular components, which characterizes weakening of somatic cell defensive reaction as a result of the prolonged action of radiation. Consequently, our experiments showed, as had investigations of the function of the reticulo-endothelial system, phasic changes in the defensive reaction of cells to virus, conditioned by the chronic action of small doses of radiation. These phasic changes indicate that, in response to initial, weak expression of radiation injury, there occurs activation of somatic cell defensive reactions including increased formation of oxyphilic components against the virus. As injury increases, we observe gradual weakening of the absorbing function of the reticulo-endothelium, and decrease in epithelial cell capacity to form defensive components.

A second criterion in the evaluation of the cell immunity of irradiation animals was investigation of their sensitivity to various bacterial toxins (Bact. perfringens, Bact. typhi, and others). We studied sensitivity changes in irradiated white mice to endo- and exo-toxins after the action of 190, 285, and 950 r at dosage strengths of 1.29 r/day. We evaluated the degree of sensitivity in irradiated and control animals through LD50 toxin determination according to Reed and Minch's method.

As a result of these investigations, we established that radiation doses at the indicated strength to total doses of 285 r decrease sensitivity in animals to bacterial toxins. Total doses exceeding this level, on the contrary, increase sensitivity to toxins. Figure 2 presents data illustrating sensitivity changes in irradiated animals to toxin Bact. perfringens at a 950 r total dosage. This means that at this radiation dose, irradiated animal sensitivity increased 1.62 times in comparison

to the control group. Consequently these data also indicate the phasic character of somatic cell sensitivity changes during the course of chronic, continuous action of relatively small doses of ionizing radiation on the organism.

Figure 2. Sensitivity of white mice to *Eact. parfringens* toxin during chronic, continuous Co^{60} irradiation of the organism (dosage strength 1,260 r/day).



On the basis of the conducted experiments, we can conclude that chronic irradiation leads to a disturbance in many aspects of cell immunity, particularly to decrease in the phagocytic capacity of leukocytes; weakening of the segregational function of the reticulo-endothelial system; decrease in somatic cell defensive function to virus penetration; and increase in sensitivity to bacterial toxins. A characteristic property of the observed weakening of cell immunity is the fact that it is preceded by a stimulation phase, emerging in the initial period of chronic irradiation, which is then followed by weakening.

Evaluating in this way the disturbance in natural immunity and the process of immunogenesis during chronic action of ionizing radiation on the organism as a whole, it is necessary to recognize that weakening of immunity touches upon humoral as well as cell immunity. A comparison of disturbances in humoral and cell immunity shows that they occur at the same time in the irradiated organism; they are initiated under the action of approximately equal total doses; and have the same direction. The depressed phase is preceded by stimulation of the organism's defensive reactions, having a compensatory character and a definitely positive meaning in the struggle against infections. Under continuing ionizing radiation, the resulting injury is not compensated, and there occurs a weakening of various aspects of cell and humoral immunity following which the organism becomes an arena for various auto-infectionary processes having a chronic course. As a result, various infection, and primarily auto-infectionary, processes serve as the main reason for organism fa-

tality, when the organism has been subjected to chronic, continuous action of relatively small doses of ionizing irradiation.

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THE PRODUCTION OF MORGAN'S TOXICOINFECTION
IN MONKEYS IN RELATION TO ACUTE RADIATION
SICKNESS

- USSR -

[Following is a translation of an article by L. A. Yakovleva, B. A. Lapin and S. M. Pekerman in the Russian language periodical Medical Radiology, vol. 7, no 8, August 1962, pages 65-68.]

At the present time it is well established that a single, massive irradiation significantly decreases the animal organism's resistance to various agents of infection, both bacterial and virus. The investigations of native and foreign writers were presented in the recently published monographs of V. L. Troitskiy and M. A. Tumanyan (1958), O. P. Peterson with co-authors (1961). Similar research on these problems in relation to monkeys has been very scarce. For example, M. A. Tumanyan, in experiments on monkeys, noted an abrupt increase in their sensitivity to dysentery during irradiation at lethal and sub-lethal doses of ionizing irradiation.

We obtained similar results in studying the course of Breslau's paratyphoid fever in relation to irradiation at sub-lethal dosage. Z. K. Stasilevich, studying factors decreasing the natural resistance of monkeys to *Salmonellas* and coli-enterites, established that during sub-lethal dose irradiation there is an increase in susceptibility of animals to coli-enterites and paratyphoid fever B, as well as a significant increase in the severity of these infections and Heidelberg's paratyphoid fever. Dysenteric and paratyphoid fever agents, however, are considered highly pathogenic for monkeys. In maintaining these animals in cages, without any experimental intervention, one can encounter the appearance of these infectionary processes in them; their occurrence often assumes the character of an epidemic outbreak. In a number of cases it is also possible to produce these infections in monkeys artificially.

We considered it useful to clarify whether susceptibility increases and the course of the illness becomes more severe only in the infections listed above (having a relatively wide "spontaneous" distribution among monkeys and artificially induced in them), or whether the observed regu-

larities/^{spread} according to illnesses produced by pathogenic stimuli. With this aim we dwelt on the experiment of producing Morgan's toxicoinfection whose stimulus, being conditionally pathogenic for monkeys, can often be found in the feces of healthy animals. Apparently monkeys rarely become ill from Morgan's toxicoinfection. In isolated cases, however, diarrhetic monkeys excrete Morgan's bacillus (Lovell, Hamerton).

In the past 7 years, monkeys of the Sukhumskiy nursery were found to have Morgan's toxicoinfection, confirmed bacteriologically, only 3 times. In this case, the disease had the character of an epidemic outbreak; 3 young monkeys less than a year old who were on artificial feeding became ill and died within several days. In relation to all autopsies on monkeys (1600) conducted during this period, death from Morgan's toxicoinfection was responsible only for 0.18%.

The clinical and pathomorphological picture in the dead animals was characterized by the development of a severe catarrhal-hemorrhagic gastroenteritis. This was accompanied by swelling of the mesenteric lymphatic nodes and enlargement of Payer's patches of the ileum. Enlargement of the intestinal lymphatic apparatus and that of the mesentery was associated with hyperemia, edema, and proliferation of lymphoid elements in lymphatic formations.

We used young Rhesus monkeys of an average age from $\frac{1}{2}$ to $1\frac{1}{2}$ years. Contamination was conducted according to the same technique used in the investigation of experimental paratyphoid infection of monkeys. The monkeys were contaminated by mouth on an empty stomach by daily agar culture in quantities of 30-50 mlrd. microbe bodies following preparatory induction, one hour prior to contamination, of 3-5 ml bull bile (depending on the age of the animal).

The attempt to infect 10 monkeys without prior irradiation was not successful. The animals remained healthy, according to clinical findings and blood indicators. For some time following contamination (from 3 to 16 days in different animals), however, there were large quantities of Morgan's bacteria in the fecal matter. Venous blood samples remained sterile. Starting with the second week the blood of all infected monkeys showed anti-bodies to Morgan's bacteria in titers of 1:200; and by the 15-16th day -- in titers of 1:800. Later we observed a decrease in anti-body titer.

Infection of 7 monkeys under the same conditions with preceding irradiation gave somewhat distinctive results. The animals were subjected to irradiation in 300 r doses on the twin RUM-3 apparatus 2-3 days prior to infection (voltage: 180 kV; current: 15 mA; dosage strength: 17 r/hour). In experiments we conducted earlier, irradiation of monkeys in doses of 250-300 r produces a very light form of radiation sickness which is clinically characterized primarily by the development of short-term, superficial leukopenia (2,500-3,000 leukocytes/ 1 mm^3 of blood).

Out of 7 irradiated and infected monkeys, 7 became ill. The illness was characterized by the appearance of a watery, fetid stool from the 2nd day following irradiation; the stool was sometimes mixed with mucus. In all the sick monkeys we observed listlessness, loss of appetite in various degrees. The diarrhea was accompanied by significant increase

in the ESR (from 18 to 46 mm/hour). The illness was accompanied by a moderate leukopenia (2,400-1,800 leukocytes/1 mm³). In four seriously ill animals (Sina, Fores, Shayim, Polchok), by the 3-4th day, one could already observe the appearance of significant exicosis in the form of a severe rolling back of the eyes and decrease in skin turgor. In 2 of these animals (Polchok and Sina) repeated vomiting was observed. On rib cage auscultation, moist rales were heard in 3 animals. The duration of the illness varied. In 2 mildly sick animals (Shusa and Yartan) the mild diarrhea (without any disturbance of the general state of the animals, and with ESR increase to 18 mm/hour) continued only 3 days. In the two monkeys who survived the illness with severe diarrhea, the illness lasted a relatively short time -- 7 and 13 days. Fecal bacteria in all animals was observed a relatively short time -- from 2 to 6 days.

The agglutination reaction from the blood serum of all irradiated animals 2½ weeks following infection gave no positive result. Two monkeys from this group (Sina and Shayim) died on the 3rd and 7th day of the illness, corresponding to the 5th and 10th day following irradiation.

On pathologic-anatomical autopsy of these animals, Morgan's bacteria was found in the contents of the stomach, and small and large intestine. In one case (Sina), the microbe was also found in lung tissue. In the monkey who died on the 3rd day of illness, we observed catarrhal inflammation of the mucous membrane of the small and large intestine, accompanied by severe swelling of intestinal loops. The mucous membrane was pink and swollen throughout. Edema and hyperemia of the mucous and sub-mucous intestinal layers were observed. Edematous villi of the small intestine were usually deprived of epithelial covering. The contents of the small and large intestine were watery. Intestinal inflammation was not accompanied by noticeable hyperplasia of the spleen and mesenteric lymph nodes. The lymph nodes were observed to have significant edema and hyperemia with severe dilatation of the sinuses. In sinus lumens we find a large quantity of macrophages in whose protoplasm there are often erythrocytes, brown pigment, and cell fragments. In some areas of the sinus lumen we found the fine network of fibrin. The quantity of cells in the cortical layer of the mesenteric and peripheral nodes was somewhat decreased; this did not, however, appear in the form of significant wasting away of lymphoid tissue. Light centers were not numerous, and were of small sizes. There was often cell degeneration with rhexis of the nucleus. The spleen was small, moderately firm, with a well-marked network of trabeculae and small follicles. The quantity of lymphocytes appeared significantly decreased. Blood vessels were usually distended. Small hemorrhages were encountered. This monkey was also suffering from focal pneumonia having a very mixed morphological character. At the same time that alveolar groups were observed filled with leukocytic exudate, alveoli were encountered with serous fluid in the lumen containing various quantities of macrophages. In some areas the alveoli were almost completely full of erythrocytes, and sometimes with fibrin. The process had the distinctive character of bronchopneumonia with leukocytic infiltration of bronchial walls and with serous-leukocytic exudate filling lumens of the bronchi. Other internal organs presented a picture

of moderate hyperemia. Under the endocardium of the left ventricle, there were a few hemorrhages.

In the second case, where the monkey died on the 7th day of illness, pathomorphological investigation showed severe gastroenteritis with severe edema of the mucous, sub-mucous, and in some places of the serous layer, as well as the appearance of a large number of hemorrhages in the stomach and along the course of the small intestine. The mucous membrane of the stomach showed small necroses. The contents of the small and large intestine were watery with pinkish-gray small flakes. In microscopic section, follicles were not distinguished.

In microscopic investigation, significant hyperemia of the organ was observed with blood overflow in the sinuses. Follicles were small. The quantity of lymphocytes in them was noticeably reduced. Light centers in follicles were found relatively infrequently. Occasionally we found here an accumulation of protein exudate. We had similar findings in the mesenterial lymph nodes where the number of lymphocytes was also clearly reduced. We found, just as in the monkey who had died on the 3rd day, that the nodes had severe distension of sinuses with an accumulation of a large number of macrophages. We very often observed erythrocytes in macrophage protoplasm, and less often — clumps of brown pigment.

These observations are evidence that the stimulus for Morgan's toxicoinfection, being for Rhesus monkeys conditionally pathogenic and not inducing in artificial infection the appearance of an infectious process, on x-ray irradiation of these animals at sub-lethal doses, produces the development of a severe process of infection concluding in a number of cases with the animals' death. The illness, appearing in relation to irradiation, does not differ as a whole from the spontaneously appearing illness, and has the character of severe gastroenteritis. Irradiation, however, imposes its mark on the morphological manifestation of this illness in the form of the development of moderate atrophic phenomena in the spleen and intestinal lymphatic apparatus.

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ESTABLISHING PERMISSIBLE MAXIMUMS IN THE
CONTENT AND INGESTION LEVELS OF RADIOACTIVE
ISOTOPES IN THE ORGANISM

-USSR-

Following is the translation of an article by Yu. I. Moskalev in the Russian-language periodical Meditsinskaya Radiologiya (Medical Radiology), Vol 7, No 8, Moscow, August 1962, pages 91-97.]

In order to establish permissible levels for the ingestion of radioactive isotopes in the organism, an understanding of general laws of biological activity for small ionizing radiation doses is necessary. Among the basic foci of radiobiology, an important place is occupied by problems of threshold, summation, restoration, compensation, and radiosensitivity in their various aspects. An understanding of laws governing distribution, accumulation, and removal of radioactive isotopes from the organism in relation to the rhythm of their ingestion -- is another, but no less important, aspect of this question.

In this article we wish to examine possibilities of experimental bases for permissible maximums in the content and ingestion levels of radioactive isotopes in the human organism, while using osteosarcomogenic and leukemogenic action of radioactive isotopes as our criterion for longevity.

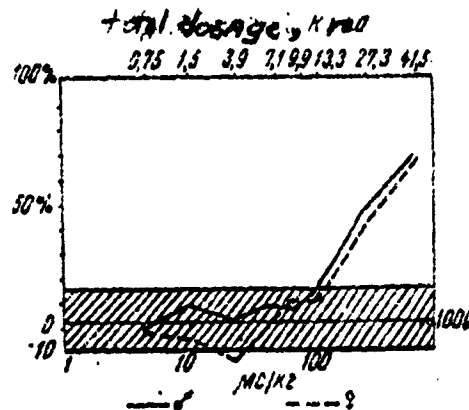
The high energy level of irradiation, significantly exceeding that of chemical ties, makes the hypothesis highly likely that there is no threshold for the action of ionizing radiation in initial changes in any structure of the organism on a molecular level. It does not follow, however, that reactions at other levels also have no threshold. Experimental evidence on the biological activity of various aspects of ionizing radiation, including radioactive isotopes, is sufficiently convincing on this score.

In resolving the problem of the threshold or non-threshold nature of the reaction, data concerning the form of the dose-effect curve are highly significant.

Figure 1 presents data characterizing the degree of decrease in the natural life span of rats in relation to the amount of Sr⁹⁰ induced into the abdominal cavity. We see that, according to the criterion of

life span duration, the action of Sr^{90} has a threshold character. Analogous results were obtained with other radioactive isotopes, as for instance Ce^{144} , Ca^{137} , Ba^{140} and others. There exists a very wide dosage diapason which does not affect the longevity of experimental rats. The maximal Sr^{90} dosage that is ineffective for rats, according to the criterion of longevity, is 25-50 $\mu\text{c}/\text{kg}$; and for mice (according to the data of M. Finkel') — 44 $\mu\text{c}/\text{kg}$.

Figure 1. The average decrease in the life span of rats (in percentages to control) in relation to the quantity of intra-abdominal induction of Sr^{90} .



Legend: The striped area — death rate for control animals with reliability intervals for $P = 0.05$.

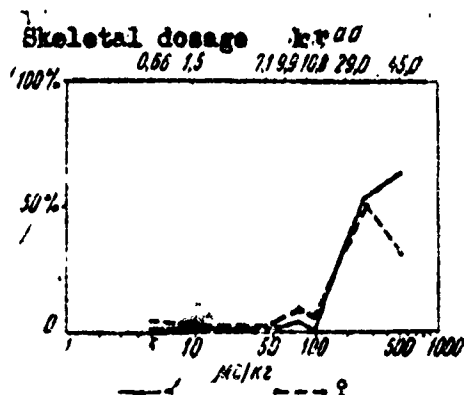
We are acquiring experimental data providing evidence that, at small quantities of radioactive substances, the average life span of experimental animals increases. For instance, on induction of Sr^{90} in quantities of 1-5 per rat, the experimental animals initially die off more slowly than the control animals. In 500 days, 36.6% of the control animals died, while on induction of 1, 2, and 5 μc the corresponding percentages were 25.8, 30.9, and 17.2%. The average life span of female rats in experimental groups was 530, 536, and 585 days; while in the control — 506 days. Analogous results were obtained with Ce^{144} . In parenteral induction of this isotope in quantities of 1, 2, 5, and 10 , by the 450th day there died 7.9, 7.7, 13.2, and 8.8% of male rats and 14.3, 12.2, 17.9, and 17.1% of female rats. In the control group, for the same time interval 21.4% male rats and 28.6% female rats died. The differences between the death rates for control and experimental groups are reliable. Radiation levels for the animals at the quantities of Ce^{144} were comparatively low. The average daily dosage strength on induction

of $1-5 \mu\text{Ce}^{144}$ was $0.84-0.4 \text{ rad/day}$, and in bone tissue $1.3-6.2 \text{ rdd/day}$. The average irradiation dose, accumulated during the life span, was $0.03-0.16 \text{ krad}$, and in bone tissue -- $0.51-2.6 \text{ krad}$. M. Finkel's research also emphasizes the long, in comparison with adequate control, life span of mice subjected to small quantities of Pu^{29} , U^{132} , and Po^{210} .

We are dwelling in some detail on this data as we are deeply convinced that in evaluating permissible levels of content and ingestion of radioactive isotopes in the organism it is appropriate to use not just any reaction of the organism to irradiation, but only those which characterize the injurious action of radiation. Of course, as a result of the fact that under conditions of prolonged action of low radiation levels average life span increase is possible, the causes of death can significantly differ from these in the control population. In this connection we are faced with the difficult problem concerning which deviations from "the norm" in conditions of continuous radiation can be taken into account in the evaluation of harmful effects of small dosage radiation.

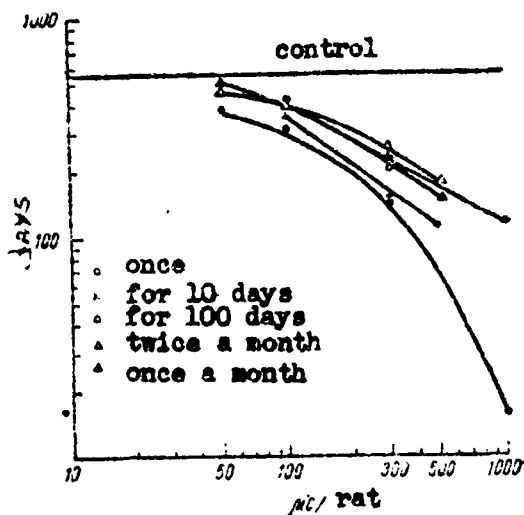
In the evaluation of the injurious action of radioactive isotopes, the data characterizing their blastomogenic activity is very significant. One of the most dangerous of the radioactive isotopes in the professional sense is Sr^{90} . Experiment shows that this radioactive isotope elicits in animals (mice, rats, rabbits, dogs) the appearance of tumors of the bone, and hemopoietic and endocrine systems. Quantitative data, describing the appearance of these tumors in relation to the quantity of induced activity, do not have a linear character. Most frequently Sr^{90} produces bone tissue tumors in animals. This type of tumor reaction has been studied in more detail and can be quantitatively described. Figure 2 shows the "threshold" nature of the indicated effect, in any case for the limited population of experimental animals encompassing hundreds of animals per dose. On single parenteral induction of the isotope, the minimal osteosarcomogenic dose is within limits of $25-50 \mu\text{C/kg}$. According to our evidence, on single parenteral induction of rats with Sr^{90} , the ineffective quantity in relation to osteosarcoma is $5-50 \mu\text{C/kg}$; according to M. Finkel's mice experiments, it is $44 \mu\text{C/kg}$. If we suppose that a similar ratio is true in man, then allowing for differences in life span, single parenteral induction of Sr^{90} in quantities of $10-100 \mu\text{C}$ should not affect the natural life span in man nor increase the incidence of bone tissue tumors.

Figure 2. The frequency of osteosarcoma in male and female rats in relation to the quantity of intra-abdominally induced Sr⁹⁰.



The action of Sr⁹⁰ often produces leukoses. The problem of whether this is a threshold or non-threshold reaction has not yet been resolved. Rats develop leukoses significantly more rarely than sarcomas under the action of Sr⁹⁰. On inducing Sr⁹⁰ in quantities of 50-250 µg/kg, the frequency of leukoses increases 2-4 times in comparison with the control. The relation of leukoses incidence to the quantity of parenteral rat induction of Sr⁹⁰ is illustrated in Figure 3. The data in this figure indicate the absence of a linear relationship between the quantity of induced Sr⁹⁰ and the frequency of leukoses. The shape of the curve is evidence of the necessity for exceeding threshold dosages in producing leukoses. In Sr⁹⁰ induction in quantities of 5 µg/kg, leukoses are encountered in the same frequency in experimental (in one rat out of 83, surviving 200 days, or 1.2%) and control rats (in 6 out of 337, or 1.8%). These rats sustain an irradiation dose of 0.27 krad in their bone marrow during their lifetime.

Figure 3. The average life span of rats in relation to the ingestion rhythm and Sr^{90} dosage.



According to the influence of radioactive isotopes on the life span and the appearance of tumors in the hemopoietic tissue and bone, the action of Sr^{90} and other osteotropic isotopes has a threshold character. This provides a basis for future consideration of the problem of permissible levels of content and ingestion for radioactive isotopes in the organism for a few people at least, whose work is related to the utilization of radioactive isotopes.

Because of the slow removal from the organism of the injurious action of radioactive isotopes, even their single ingestion into the organism continues over a very prolonged period; and in the case of long-lived radioactive isotopes — over a full life span. It is therefore very important to clarify the question of the role of the time factor in the injurious action of radioactive isotopes, and the relationship of their biological activity to the ingestion rhythm of the organism.

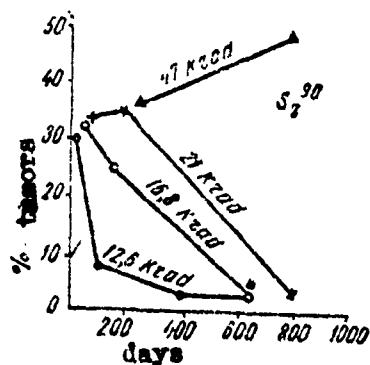
A very complex correlation exists between the organism's reactions and ionizing radiation's action rhythm. At the basis of the correlation lies the differing sensitivity of separate systems and organs to irradiation, and their varied capacity for compensation, restoration, and summation of irradiation injury. Restorative processes occur differently in various systems of the organism, so that a decrease of dosage strength can have unequal significance for various systems. Ovaries have a very high sensitivity to ionizing irradiation and a very low reparative capacity. In contrast to hemopoietic organs and the intestinal mucous membrane, the ovaries show destructive changes of a single type on single massive, and prolonged, action.

A comparative evaluation of the action of $Sr^{89,90}$ on the life span of rats in relation to the isotope ingestion rhythm indicates incomplete summation of radioactive effects. Protracted induction (daily for 100 days at $15 \mu c$) of highly effective single doses ($1,500 \mu c$ per rat, intra-abdominally) of $Sr^{89,90}$ leads to a significant decrease (by 10 times) in comparison with the control (478 ± 21 days) of the life span (from 19 ± 4 at a single induction to 160 ± 20 days at prolonged ingestion). It is important to emphasize that such an abrupt decrease in the effective action of radioactive isotopes on protracted ingestion into the organism is observed only under the breakdown of highly effective quantities. On breakdown of acute and chronic effective isotope quantities, differences in the life span in relation to isotope ingestion rhythm are less marked (See figure 3). In later intervals of the experiment there are similar peripheral blood changes in the animals, irregardless of single or prolonged induction of the indicated quantity of Sr^{90} .

It is of interest to evaluate the significance of dosage strength in the occurrence of histogenic action from ionizing radiation. An analysis of experimental data shows that, under the action of Sr^{90} , the incidence of osteosarcom significantly depends on dosage strength (Figure 4) [See Note]. Within limits of equal total doses ($12.6-21$ krad), decreasing dosage strength by 20 times produces a decrease of osteosarcoma incidence by 10 times. When the bone marrow accumulates 12.6 krad for 30, 100, and 400 days, osteosarcomas occur in 30; 8, 4, and 2.6% of the animals. Within limits of optimal osteosarcomogenic doses (47 krad), decreasing the irradiational dosage strength by 3 times has little reflection on the total incidence of osteosarcomas.

[Note]: Text of footnote: The frequency of osteosarcomas under the given total irradiation dosage was not determined immediately after the bone marrow accumulated a corresponding dose, but after the "latent" period elapsed (200 days) necessary for development of the tumor. Thus, for example, at total doses of 16.8 krad accumulated by the skeleton over 50 days, the osteosarcoma frequency induced by this dosage was determined on the 250th day, i.e. after completion of the "latent" period.)

Figure 4. The relation of the incidence of sarcomas in rats under the action of Sr^{90} to the strength and magnitude of the total irradiation dose in bone tissue.



Corresponding to these data are the experiments on the study of the relationship between osteosarcomogenic Sr⁸⁹ action (Kusma and Zander, 1958) and Sr⁹⁰ (Yu. I. Moskalev) in relation to the isotope ingestion rhythm of the organism. In our experiment, conducted with V. N. Strel'tsova, it was established that in single Sr⁹⁰ induction (in equilibrium with Y⁹⁰) at quantities of 100 μc per rat, osteosarcomas develop in 26%; on induction of the indicated quantity for 100 days — in 8.3%; and on fractional induction at 2 week intervals (for 10 inductions) and one month (5 inductions), the rats did not develop osteosarcomas. We must state that the "latent" period necessary for the development of osteosarcomas increases with a decreased quantity of induced activity.

These facts are evidence that, under low radiation levels in structures where deleterious changes are occurring, restorative processes take place. This means that radiation summation is incomplete. Under the action of α -radiation, bone tissue restorative processes occur much more weakly than under β -irradiation. For example, according to the observations of M. Finkel' (1956), under the action of Ra²²⁶ a decrease to 1/10th (from 60 to 5 $\mu\text{c}/\text{kg}$) of the amount of induced isotope (in experiments with mice) leads to a decrease in incidence of osteosarcoma from 60 to 35%, i.e. it lessens to half. In the case of Pu²³⁹, on decrease of the optimal osteosarcomogenic dose from 3 to 0.3 $\mu\text{c}/\text{kg}$, the frequency of osteosarcoma decreased to 19%. Research on Pu²³⁹, conducted on rats by A. M. Bukhtoyarova and V. K. Lemberg, shows that under a decreased quantity of induced activity to 1/10th (from 6.3 to 0.63 $\mu\text{c}/\text{kg}$) the frequency of osteosarcoma decreases to 40%. There is an utterly different correlation under the action of β -irradiation (Yu. I. Moskalev). A decrease to 1/10th of optimal osteosarcomogenic quantities of Sr⁹⁰ and Ce¹⁴⁴ (from 50-1,000 to 50-100 $\mu\text{c}/\text{kg}$) is associated with a drop in frequency of osteosarcoma to 3.3-2%, or to an order higher than under α -irradiation.

Table 1. Bone tumor frequency under parenteral induction of Pu²³⁹ under various isotope ingestion rhythms (according to the data of Yu. I. Moskalev, L. A. Buldakov, and V. N. Strel'tsova)

Изотоп 2.	Количество, $\mu\text{c}/\text{kg}$ 3	1. Ритм введения				
		однократно 4	за 50 дней 5	за 100 дней 6	один раз в неделю 3-9 недель 7	один раз в 2 недели за 18 недель 8
Pu ²³⁹	1,25-20	2/46 (4,4%)	4/45 (8,9%)	3/45 (6,7%)	5/36 (13,9%)	3/20 (15%)
Sr ⁹⁰ +Y ⁹⁰	500	6/23 (26%)		1/12 (8,3%)	0/14 (0)	0/11 (0)

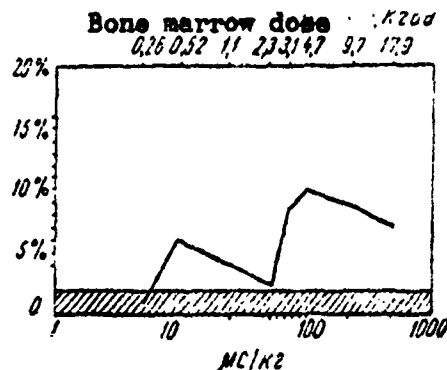
Legends: 1. Induction rhythm. 2. Isotope. 3. Quantity $\mu\text{c}/\text{kg}$. 4. single 5. for 50 days 6. for 100 days 7. once weekly for 9 weeks 8. once in 2 weeks for 18 weeks.

Notes: the numerator — tumor frequency; the denominator — the quantity of animals not surviving after the 200th day.

In contrast to Sr⁹⁰, the osteosarcomogenic action of Pu²³⁹ is not too dependent on the ingestion rhythm of the isotope into the organism. It was shown that under Pu²³⁹ action bone tumors occur both with single and prolonged ingestion of equal isotope amounts (Table 1).

One forms the impression that, under prolonged induction of Pu²³⁹, bone tissue tumors develop even somewhat more frequently than under single induction. For example, after single induction of Pu²³⁹ in quantities of 1.25 to 20 μ c, bone tumors developed in 40% of the rats who did not survive after the 200th day; on induction of the same quantities for 50 and 100 days, 9 weeks (once weekly) and 18 weeks (once every two weeks), bone tumors developed correspondingly in 8.9, 6.7, 13.9, and 15%. Since our data are quantitatively small, further experiments according to this plan are necessary on a larger sample of animals. Nevertheless, results of our research permit our making the conclusion that the frequency of bone tumors on fractioned and protracted induction of α -irradiators does not, in any case, decrease. These data are evidence that injury produced by α -irradiators are less well restored and better summated under protracted action. The indicated differences in blastogenic activity of α - and β -irradiators is a necessary factor to consider in attempts to extrapolate from experimental results on animals to humans.

Figure 5. The relation of leukoses frequency to the quantity of induced Sr⁹⁰.



Legend: Striped area — leukoses frequency in control rats.

In contrast to osteosarcomas, the frequency of hemopoietic tissue tumors under Sr⁹⁰ in conditions of protracted action does not decrease. On the contrary, it can even be greater than in concentrated action. For example, at total doses of 2.7 krad accumulated by bone marrow over 50 days, leukoses under Sr⁹⁰ developed in 1% of the rats; under accumulation of the indicated dose for 200 and 600 days — in a corresponding 3.8 and 5.6% of animals. At total dose of 5.6 krad, leukoses frequency at accumulated doses for 50, 150, and 650 days was 2.5, 4.5 and 8.3% (Figure 5).

These facts point to the existence of summation and poor restoration of injuries in bone marrow cambial elements leading to the occurrence of leukoses.

The data we have examined lead us to the conclusion that under prolonged ingestion of small quantities of Sr^{90} , the probability of the occurrence of osteosarcomas decreases. The existence of a definite "threshold" dose, necessary for the induction of sarcomas, and the abrupt decrease in the frequency of bone tumors under decreased dosage strengths, provide a basis for the position stated above. The existence of more complex conditions for the occurrence of leukoses, the existence of a "threshold" dose, and the poor restoration of injuries in bone marrow cells as a consequence of the significantly longer human life span do not exclude the possibility of the occurrence of this reaction under smaller Sr^{90} quantities than those for rats. It is obvious that future accumulation of experimental data is necessary to pin-point minimal leukemogenic doses and the role of the time factor in the production of this reaction.

Leukemogenic radioactive isotope action cannot be examined apart from other reactions of the organism. If we use, as such an additional criterion, the average life span of rats dying from leukosis in the control and experimental groups, then induction of minimal leukemogenic quantities of Sr^{90} ($2\mu\text{c}$ per rat) produces leukoses in 5 out of 82 rats (6.1%). The average life span of rats with leukoses was 591 days and was even somewhat longer than in control animals (538 days).

Taking Sr^{90} as an example, we will examine ways of translating experimental data from animals to humans. The experimental data indicated above concerning the effect of Sr^{90} on the life span and on the occurrence of tumors of the bone and hemopoietic system can be utilized for the evaluation of minimal permissible levels of the ingestion of this isotope by the human organism. They show that single parenteral Sr^{90} induction in $10\mu\text{c}$ quantity does not affect the natural life span or the frequency of bone tumors and leukoses in the human. In recomputing experimental data from animals to humans, owing to the significant differences in longevity, the quantity of Sr^{90} that is non-effective for rats decreases to 2.85%. This means that the same decrease holds for the irradiation dose strength in the rat's organ. For reactions (longevity, bone tumors) which are well restored and weakly summated under protracted action, this has great importance as the additional biological coefficient of reserve plays a part here. For those reactions whose development is little affected by decrease of dosage strength (leukoses, ovarian injuries), this circumstance apparently will have less meaning.

The bone tissue has a prolonged retention not of all the strontium, but only of a portion of it. An analysis of data on distribution shows that rat bone at final stages of the experiment retains 15-20% of the induced Sr^{90} . The maximal permissible Sr^{90} content in human bones, therefore, should be $1.5-2\mu\text{c}$. A similar magnitude ($2.3\mu\text{c}$) was obtained in computing the maximal permissible Sr^{90} content in the human body by empirical equation.

$$(1) \text{ Mpc} = 4.6 \text{ d}$$

where M_{pc} is the maximal permissible content of osteotropic isotope in the human skeleton; d is the optimal osteosarcomogenic irradiation dose for rats (in microcurie per 1 g).

Equation (1) is derived from the comparison of clinical and experimental investigations on osteosarcomogenic action of radium.

Table 2.

Изотоп	Максимальное содержание при интраперитонеальном облучении, $\mu\text{c/g}$	Предельно допустимое содержание изотопа в скелете человека, $\mu\text{c/g}$
Sr^{90}	0,5	2,3
Sr^{90}	1,0	4,6
Ba^{140}	1,6	7,5
Y^{91}	1,0	4,6
Y^{90}	3,0	14
Ca^{45}	0,5	2,3
Pm^{147}	3,4	15,8
La^{140}	10,3	45
Pu^{239}	0,005	0,023

- Legend: 1. isotope
 2. optimal osteosarcomogenic content on intraperitoneal induction, $\mu\text{c/g}$
 3. maximal permissible isotope content in the human skeleton, $\mu\text{c/g}$.

Table 2 presents magnitudes of maximal permissible contents derived from equation (1) for a number of reactive isotopes in the human body.

The magnitudes of maximal permissible radioactive isotope content thus found are in correspondence with international recommendations.

In evaluating the maximal permissible Sr^{90} content in the human skeleton derived through other methods, including dosimetry, taking into account the unequal distribution of the isotope in the bone tissue and the differences in the magnitudes of local tissue dosages connected with this, we obtain similar magnitudes (1.8-3.7 μc). On conducting corresponding computations for the maximal permissible strength, we used a dosage equal to 300 mber/week.

Once the magnitude of maximal permissible radioactive isotope content has been established in the critical organ, we can go on to an examination of the problem of the activity amounts that can be ingested daily by the organism with food products or through respiratory channels. Until the present time, information on the continuous deposit and removal of radioactive isotopes from critical organs has been gleaned primarily from investigations of single inductions of a substance. Recent research, however, indicates that this method of evaluating maximal permissible levels of radioactive isotope ingestion by the organism is not effective.

We will illustrate this through taking Sr^{90} as an example. In ex-

periments with intra-peritoneal induction of rats, it was found that after single induction, its removal from bone tissue can be satisfactorily described by the equation:

$$(2) \quad Q_t = 25.5 e^{-0.017t} + 36.6 e^{-0.0018t}$$

Moreover 41% of the initial Sr⁹⁰ deposit is removed with T_{biol.} = 40 days and 59% — with T_{biol.} = 392 days.

In conditions of prolonged ingestion (daily induction for 100 days) there are changes not only in the constant removal of the isotope from bones, but, what is particularly important, there are changes in the coefficients of Sr⁹⁰ storage in the bone tissue. Equation (3) describes changes in Sr⁹⁰ content in rat skeleton after isotope induction is stopped:

$$(3) \quad Q_t = 8.6 e^{-0.009t} + 18.5 e^{-0.00015t}$$

Nearly 32% of Sr⁹⁰ is removed with T_{biol.} = 77 days, and 68% — with T_{biol.} = 14, 600 days (the magnitude is apparently over-estimated; the observation period after cessation of induction was only 340 days). In comparison with single induction at prolonged ingestion, the magnitude of Sr⁹⁰ storage in the skeleton was 43.5% lower. On fractional induction of Sr⁹⁰ (once a month for a total of 5 inductions), its removal from the skeleton (after cessation of induction) is described by the equation:

$$(4) \quad Q_t = 13.9 e^{-0.0264t} + 17.1 e^{-0.00041t}$$

Nearly 46% of the activity is removed with T_{biol.} = 26 days and 54% — with T_{biol.} = 1,690 days. In comparison with single induction, Sr⁹⁰ content was 50% less.

The indicated data is sufficiently clear evidence that the constant bone deposition and removal of Sr⁹⁰ depends on the rhythm and ingestion of isotope induction into the organism. Moreover the magnitude of Sr⁹⁰ deposition in bone tissue, in conditions of prolonged ingestion, significantly decreases. As a result of the constant deposition and removal of Sr⁹⁰ from the skeleton depending on the rhythm of its induction into the organism and changes in time, it would be inadvisable to draw conclusions regarding laws of isotope deposition in the organism on the basis of experimentation with single induction. There is an obvious necessity for direct data on the patterns of radioactive isotope deposition under prolonged ingestion into the organism.

Under prolonged ingestion of radioactive substances, as a result of radioactive breakdown and removal, an equilibrium is established between isotope ingestion and retention in the organism. Apparently deposition multiplicity (the relation of isotope retention in the organism in a critical organ after an equilibrium has been established to the daily ingested dose) and the speed with which various isotopes achieve an equilibrium will differ. In the case of isotopes having a short period of partial breakdown (for example, Sr⁸⁹ with T_{1/2} = 53 days), but a long period of removal from the organism, the problem is resolved re-

latively simply, as their deposition multiplicity in the organism is determined by the partial breakdown period, and the equilibrium between ingestion and deposition of the isotope in the organism is established relatively quickly. The research of E. B. Kurlyandskiy and co-authors (1957) and D. I. Ilyin and Yu. I. Moskalev (1959) conducted on various animals confirms this position. It appeared that Sr^{89} deposition multiplicity in the bone tissue of rats and rabbits is 8.4, and the equilibrium between isotope ingestion and retention in bones was established by the 130th day. Subsequent daily Sr^{89} induction over 830 days did not affect the magnitude of deposition multiplicity of this isotope in the skeleton. On the basis of these data, it is not difficult to calculate that for retention in human bones of maximal permissible Sr^{89} content ($2\mu\text{C}$), there can be daily ingestion of $0.2\mu\text{C}$ of this isotope. In the case of long-lived radioactive isotopes which are slowly removed from the organism, including Sr^{90} , the equilibrium between ingestion and deposition is established at later intervals.

By means of calculations, we found, along with D. I. Ilyin, that in pigs and dogs, on daily Sr^{90} ingestion, per os equilibrium (99%) must be established in approximately 1,300 days, while the isotope deposition multiplicity is equal to 45. A similar magnitude for Sr^{90} deposition multiplicity in the skeleton, 15, was obtained in experiments on dogs by L. N. Burykina, inducing animals with Sr^{90} by mouth over a period of several years. In conditions of continuous ingestion through the gastrointestinal tract, the Sr^{90} deposition multiplicity in the human skeleton would apparently differ little from the magnitudes indicated above, particularly in the case where Sr^{90} would be ingested by an adult human.

The indirect data confirms the accuracy of the indicated position. We will therefore utilize data on the deposition of stable strontium in the human organism. We know that man consumes 10^{-3} g of stable strontium with his food per day, while the whole human organism retains 0.14 g of this isotope. It therefore follows that under prolonged ingestion, the strontium content in the whole skeleton will exceed the daily ingested quantity by 140 times. A similar magnitude of Sr^{90} deposition multiplicity in the human skeleton is obtained in the comparison of the exchange characteristics of the indicated element with stable calcium. We know that the passage of Sr^{90} from food into bone is achieved with its discrimination in relation to calcium. On the basis of the research of L. A. Buldakovskiy and Yu. I. Moskalev (1960) conducted on sheep, as well as direct observation of the migration of Sr^{90} falling on the earth's surface along the food chain (milk -- bones of new-born children), this coefficient is determined to be 0.2-0.25. These data are evidence that, in comparison with calcium, Sr^{90} is ingested and retained by the organism in smaller amounts.

Sr^{90} deposition multiplicity in the human skeleton will apparently be smaller by the magnitude of its discrimination in relation to calcium. Since calcium deposition multiplicity is 1,000, the corresponding magnitude for Sr^{90} should be 200-250. Such Sr^{90} deposition multiplicities might be observed if the isotope had been ingested by the organism from childhood. When Sr^{90} is ingested by the adult human, its deposition

multiplicity should be lower than these magnitudes and similar to that obtained in experiment. If we take as a base a maximal Sr^{90} deposition multiplicity of the human skeleton of 250, then for the skeleton to retain the maximal permissible magnitude ($2\mu\text{c}$) of this isotope there must be a daily induction of $0.008\mu\text{c}$. This magnitude is 4.4 times higher than the one recommended by the International Commission on radiological protection ($0.0018\mu\text{c}$).

On this basis we can conclude that existing norms of maximal permissible content and ingestion of Sr^{90} in the human organism have experimental verification and indicate the existence of a sufficient reserve guarantee.

The induction of maximal permissible Sr^{90} quantities into the organism cannot present great dangers in the genetic sense. In any case, this danger is significantly less than that from the naturally radioactive isotopes K^{40} and C^{14} which constantly enter the organism with food intake. For example, the adult human daily takes in $0.0054\mu\text{c}$ of naturally radioactive isotopes K^{40} and C^{14} , which is 3.2 times greater than the maximal permissible magnitude of Sr^{90} ingestion ($0.0018\mu\text{c}$). In comparison of the indicated magnitudes, we must keep in mind that K^{40} and C^{14} are wholly ingested from the gastro-intestinal tract and are comparatively evenly distributed in organs and tissues, while Sr^{90} is only partially ingested from the gastro-intestinal tract and is selectively retained by bones, when soft tissues retain only an insignificant portion.

The data cited indicate that further research is necessary, directed at studying the radiobiological laws of the action of ionizing radiation in small doses; establishing permissible retention levels (in the critical organ) of radioactive isotopes and their ingestion by the human organism; and studying the laws of their deposition and removal under prolonged ingestion by the organism.

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THE SECOND ALL-UNION CONFERENCE ON THE APPLICATION
OF RADIOELECTRONICS IN BIOLOGY AND MEDICINE

- USSR -

Following is the translation of an article by Yu. B. Mendel'tsvay in the Russian-language periodical Meditsinskaya Radiologiya (Medical Radiology), Vol 7, No 8, Moscow, August 1962, pages 100-101.

From April 24-28, 1962 there was held in Leningrad the Second All-Union Conference on the application of radioelectronics to biology and medicine, sponsored by the Scientific Technical Society of Radio-technics and Electrosignals Imeni A. S. Popova; the Ministry of Public Health USSR; the All-Union Scientific Council on Radiophysics and Radio-technics AS USSR; the State Committee of the Council of Ministers USSR on radioelectronics; and the Academy of Medical Sciences USSR.

More than 1,000 people participated in the conference. Four plenary meetings were held at which 11 reports were made on the major problems of the application of electronics in medicine and biology; the role and future for the utilization of cybernetics, electronic microscopy, television techniques, ultra-sound, radioelectronics in physical therapy; and the development and production of electronic medical equipment in the USSR was discussed.

At 11 sectional meetings, more than 100 reports were made. One of the sections was devoted to electronic equipment in physiological research using isotopes.

G. A. Malov and N. A. Gabelova reported on the results of the study of blood flow speeds in various areas of the vascular canal in patients with acquired and hereditary heart defects, as well as in patients with vascular diseases. There were 600 people studied in all. The research was conducted with the aid of an 8-canal radiograph in the Institute of Heart and Vascular Surgery. A comparison of obtained speed magnitudes of blood flow at various areas of the vascular canal with some hemodynamic indicators provides the possibility for establishing laws which do not emerge in the study of blood flow speeds through usual methods.

The report of E. Yu. El'kind and I. M. Gofmen described the gamma-

topograph having graph registration, developed in the All-Union Scientific Research Institute of Medical Instruments and Equipment of the Ministry of Public Health USSR (ASRIMIE), which has been approved clinically by the Institute of Neurosurgery imeni Acad. N. N. Burdenko (F. M. Lyass) and the Oncological Institute imeni P. A. Gertsena (M. A. Volkova).

S. G. Zen'kovich's report on problems of gammatopography concerned chiefly the diagnostics of brain tumors. He reported on the basic characteristics of the gammaencephalograph of the Leningrad Neurosurgical Institute imeni A. L. Polenova; briefly surveyed foreign models; and also examined the problem of the further development and refinement of the method of scintillating gammatopography.

V. A. Belyakov (ASRIMIE) discussed radiometry of biological liquids -- equipment planned for the determination of urine-excreted radioactive iodine (J^{131}) and other γ -active isotopes utilized therapeutically, without additional dilution and evaporation.

Yu. B. Mandel'tsbayg and I. K. Tabarovskiy (ASRIMIE) reported on the clinical scintillating equipment for the determination of thyroid function by means of J^{131} . For wider inculcation into clinical practice of this more highly approved radiodiagnostic technique, it is necessary: to supply the clinic with special radiometric equipment of high sensitivity which would secure a large output at sufficiently simple operating conditions; to secure the production of gelatin capsules with packaged amounts of J^{131} , obviating the necessity for the clinic to dole out the J^{131} solution into diagnostic portions. The development of this equipment should assist resolution of the first task. In 1962 the Council of National Economy in Kiev began a serial distribution of the diagnostic scintillating equipment type DSU-60.

V. A. Volkov and E. G. Gulyaeva (ASRIMIE) discussed equipment for the diagnosis of malignant neoplasms in body cavities with the aid of radioactive β -irradiators. A series has been developed of scintillating and gas-discharging β -probes for research into activity accumulation in cavities, tissues, and skin surfaces. β -probes permit diagnostic investigation of the vagina, cervix uteri, larynx, eyes, brain, esophagus, stomach, and skin.

The application of electroencephalography and methods of radioactive indices in the analysis of pharmacological activity of cholinolytic substances was the subject of A. M. Kats' report (Leningrad affiliate ASRIMIE). With the aim of studying changes in the central nervous system occurring under the influence of substances with a central cholinolytic action, research was conducted on the bioelectrical activity of the cerebral cortex in rabbits. The central cholinolytic substances used were amytil and its sulfur-containing analogue. The latter was marked S^{35} . Experiments were conducted on animals with chronically implanted platinum electrodes. Electric potentials were registered on the multi-channelled electroencephalograph ink recording. Parietal and occipital biotics were registered. At the same time, the distribution character of the amytil sulfur-containing analogue in the animal organism was studied. Combining methods of electroencephalography and radioactive indices permitted following the finest changes occurring in the central nervous sys-

tem; the control of localization and duration of their existence in the organism; and the pathways and speed of removal of the medicinal preparation. Research was conducted on many kinds of animals.

On the whole, the Second All-Union Conference on the Application of Radioelectronics to Biology and Medicine was significantly more representative than the First All-Union Conference, held in Moscow in January of 1959. This is seen even through attendance numbers (400 people in 1959) and reports presented (50 in 1959), which reflects the significant extension of the development of radio-equipment and the application of modern methods of radioelectronics in medical and biological research. Sectional meetings were very well attended, as a rule, and were very active.

However, everything said relates very little to the section on electronic equipment for physiological research with the application of radioactive isotopes. This section was listless and poorly attended. Except for the concluding report of the sectional chairman, A. F. Gorodetskiy, there was no discussion of reports. Apparently the facts presented in the reports did not reflect the actual situation in the area of radiometric equipment development for medical and biological purposes. This is connected with a number of reasons. First of all, few organization of a corresponding profile were urged to attend (5 out of the 7 sectional reports were presented by the ASRIMIE). Sectional reports had differing orientations: in some the main emphasis was on purely technical and physical problems, in others -- on medical ones. They were therefore intended for differing types of audience. Since problems of a medical character (the technique of utilizing radioactive isotopes, clinical and experimental results) are chiefly discussed at all-union and republic radiological conferences, it would be advisable to concentrate the focus of subsequent conferences on the application of radioelectronics to biology and medicine on technical and physical problems in the development of radiometric equipment for medical and biological research, and the people presenting reports should be oriented accordingly. And finally, at the same time that sections were held on the indicated research, there were sectional meetings on electronic methods of research into physiological function, and sections on the application of television to biology and medicine; this led to some measure of a dissipation of effort.

There was great interest in the exhibit of new radioelectronic equipment designed for medicine and biology, held at the conference. The exhibit demonstrated more than 150 appliances and instruments (in 1959 only 90 exhibits were shown), developed and prepared by the ASRIMIE, the factory "Krasnogvardeyets", the Scientific Research Institute of Experimental Surgical Equipment and Instruments, the constructional bureau "Biofizpribor" and many other organizations.

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