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THE INFLUENCE OF LOW DOSES OF IONIZING RADIATION ON BIOLOGICAL SYSTEMS

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THE INFLUENCE OF LOW DOSES OF IONIZING RADIATION ON BIOLOGICAL SYSTEMS.

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Abstract:

Recent results concerning possible beneficial effects of low doses of ionizing radiation on biological systems are summarized. It is also pointed out on the basis of existing evidence that harmful effects on living organisms take place not only in the case of excess but also in the case of deficiency of ionizing radiation. Possibility of using radio-enhanced ultralow luminescence for studying hormesis phenomena is discussed.

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1. Introduction.

It has been regarded until almost recent times that ionizing radiation is harmful to living organisms independently of magnitude of its dose. This was caused predominantly by the fact that radiation effects were estimated by models based on the lineer hypothesis which assumes that all radiation is harmful. This concept has been accepted as a fact and become a basis for calculating low level effects by extrapolation from high-level data. The estimates of this kind remain however in contradiction with observed low-level dose-response data that indicate a negative correlation between low-level radiation and harmful health effects. This fact places ionizing radiation among variety of agents which are harmful in high-level doses yet which are stimulating or even necessary at low doses. In such a list there are among others: sunlight, vitamine D, certain antibiotics, various metals, caffeine and insuline. The negative correlation between low-level radiation data and health effects is the basis of evidence supporting the validity of hormesis phenomenon. Hormesis is the positive stimulation by subharmful quantities of any agent to any biological system [1]. It prediots that while high levels of exposure to ionizing radiation is hazardous, minute doses can be stimulating and beneficial. They can improve growth, development, reproduction, life span as well as resistence to subsequent radiation and infection. Radiation stimulation extends the Arndt--Schultz law of toxycology: small doses of poisons are stimulatory. This is particulary applicable to organisms in suboptimal condition.

Hormesis with ionizing radiation has been known sice several decades. For a long time authors were sceptical of their results when they found that organisms exposed to low level radiation exhibited longer life span, higher resistance against infection etc. than controls. Twenty years ago Henry [2] published a paper under the title "Is all nuclear radiation harmfull?" in which all existing data on chronic low level exposure to a variety of animals are summarized. He presented the hypothesis that low level of radiation is not harmful and may be beneficial. Unfortunately this paper has not received much attention by that time. At present the accumulated evidence for hormesis with ionizing radiation is enormous. Luckey [1] who in 1980 collected and systematized existing data until 1977 has quoted more than 1000 published reports supporting beneficial effect hypothesis. Last years brought many new contributions to this subject [3 - 14].

The purpose of this paper is to summarize briefly present status of this subject without entering into to many details and its content is as follows. In Sec.2 the notion of the dose-response curve is introduced. Section 3 is devoted to the background ionizing radiation. Some of the examples of the dose--response function are presented in Section 4. This Section contains brief summary of data concerning influence of low-level radiation upon plants and animals. Section 5 summarises available information concerning effects of low level ionizing rediation on human beings gathered mainly from observation of populations living in regions of increased level of background radiation. Possible role of ionizing radiation for some physiological functions of living organisms is considered in Section 6. Finally summarising discussion is given in Section 7.

2. The dose- response curve.

The notion of ionizing radiation concerns any radiation which when interacting with biological molecules causes their fragmentation to ions, radicals or unbounded atoms. Thus to ionizing radiation one can include electromagnetic radiation of frequency greater than 10^{15}Hz that is short wave ultraviolet radiation, Roentgen and gamma radiation as well as corpuscular radiation of suitable energy. In what follows the term radiation will denote electromagnetic radiation with sufficiently high energy.

Table 1. LD_{50}^{30} doses.

Subject	kR
Man	0.4
Rat	0.67
Rabbit	0.79
Fish	1.8
Snail	14.0
Yeast	30.0
Amoeba, cabbage, radish	100.0
Paramecium	300.0

Large doses of ionizing radiation are undoubtfully harmful for living organisms. Effects of large doses on living organisms are characterised by values LD_{50}^{30} defined as exposure for total body which within 30 days cause death of 50% irradiated members of the given species. Comparison of the amount of LD_{50}^{30} for different species indicates /see Table 1/ that radiosensitivity increases with philogenetic position [1,15] . The small radiation doses are understood as being equal 10 to 1000 times smaler than harmfull doses.

A hypothetic dose-response curve is illustrated in Fig.1. It illustrates qualitative changes in response to different doses of ionizing radiation. Hormesis takes place in the region located to the right of the ordinate axis where response is greater than that of controls. The abbreviation ZEP refers to zero equivalent point and indicates dose for which response is indistinguishable from controls. Doses which are greater than ZEP are harmful. Dose equal to zero corresponds to ambient radiation. Part of the curve to the left of the dose equal zero corresponds to a situation when doses are smaller than natural background.

Most experimental work has been done with low doses of X-rays and γ-rays. Different kinds of irrediation that is external and internal, chronic and acute have been used. Complete list of references concerning this subject can be found in [1,4] .

3. Background ionizing radiation.

Background radiation is the normal continuous radiation from the environment. The sources of this radiation can be external and internal. External radietion includs cosmic and terrestial rediation, radiation from air and water, from nuclear and conventional plants, from food, medical therapy and technical devices. Main source of internal radiation is the isotope ^{40}K accumulated in tissues and organs of human body. Amount of this and of others radioactive isotopes which determines contribution of internal radiation to the total dose depends upon amount of those isotopes entering into composition of food, air and water. The average total whole body ambient radiation for man has been estimated by several authors and in particular it was found by Luckey [1] to be equal around 400 mR/year. This is more than twice the limit set for man by agencies that do not usually include endogenous radiation from food and from various sources used in medicine. The Table 2 illustrates contributions of various sources of the ionizing radiation to the total dose.

Table 2. Total radiation for man.

Source	mR/year
Cosmic	55
Earth and housing	55
Instruments	28
Food and drink	30
Air and air travel	6
Fallout	4
Nuclear plants of all kinds	0.1
Medical	180
Endogenous	69
Occupational	1
Total	428

It is important to notice that the exposure for medical purposes /diagnosis and therapy/ is and probably remains a major contribution to the background ionizing radiation. Widespread use of colour television sets and of computer monitors is becoming also an important factor in increasing amount of exogenous radiation since the accompanying X-rays radiation gives substantial contribution to the total dose. Moreover flights on high altitudes can significantly increase the dose of cosmic radiation compared to that on earth. The estimates suggest [1] that a jet passenger receives 1mR/hour.

Those facts listed above justify sufficiently necessity and usefulness of studying with more detail possible effects of small doses on living organisms.

4. Investigation of hormesis with ionizing radiation for plants and animals.

First studies in this direction have concerned investigation of the influence of small doses of X-rays on algae. In 1898 Atkinson [16] observed that irradiated algae grew faster than nonirradiated controls. Since that time thousands of experiments have been performed in which representatives of virtually all known plants species were exposed to ionizing radiation. Results obtained in those experiments made it possible to conclude that small doses improve germination, cause acceleration of growth rate and development, induction of early and longer flowering, induction of rooting from stems and increased harvest. Icreased resistance of plants which grew from irradiated seeds against infection has been also reported. Majority of experiments was performed in phytotrons with strict control and applying both external and internal sources. In the case of external source one exposed seeds, bulbs and green parts of plants. Fig.2 shows the dose-response curve measured for wheat and for strawberries [1] . In both cases influence of X-rays on harvest was studied. In the case of wheat the seeds were irradiated while in the case of strawberries their plantlets. Increased yield from irradiated plants can reach about 200% for wheat and 120% for strawberries if compared with controls. Similar results were obtained in experiments parformed during space flight with onions and fungi where the plants were exposed to incresed dose of cosmic radiation. Internal irradiation of plants has been performed by supplying radioactive elements together with water or through fertilizers with appropriate admixtures. Observed effects in this case support occurence of positive stimulation of small doses of ionizing radiation. As an example one can quote experiments of Kuzin [17] where influence of small doses on harvest of cultivated plants has been observed for several years. Extensive studies of plants growth have focused upon practical application of low doses of ionizing radiation for increased production. Yet another example which one can mention on this occasion are results achieved for potatoes [1] : low doses of ionizing radiation shorten dormancy period so that one can get more than one crop per season. Careful and cautious attempts to apply radiostimulation in agriculture are practiced in very few countries only. Majority of this applications is being conducted using ^{137}Cs and ^{60}Co isotopes with beta radiation filtered out.

Appearance of stimulating effect of low doses of ionizing radiation on animals is very well documented too [1,4] . Similary to the case of plants, animal organisms were also exposed to radiation from external sources or the active elements were being added to food. Hormesis phenomenon manifested itself in increased growth rates, life span, disease resistance, reproductive capacity and resistance to larger doses of radiation. Increased growth rates have been reported for chronically irradiated animals both invertebrates and vertebrates. For instance for the X-rays doses in the range 1R/day growth rate for mice reached 130% [1] in comparison with control group /see Fig.3/. Some studies show that radiation stimulation of neurologic function takes place: irradiated mammals show increased cerebral blood flow and excitability of brain and nerves [4,18] . It has also been observed that animals which had earlier been exposed to low doses of ionizing radiation were more resistant to challenge infection than their unirradiated controls [1] . Preexposure to radiation increased also resistance to subsequent lethal doses of radiation. Inceased skin healed faster when animal had been previously irrediated. Researches also reported that animals produced more antibodies when they were irradiated. The results of several studies show that animals exposed to low doses of ionizing radiation exhibit increased average life span. This would rather be expected to occur under condition which improved defense system of living organism. Many authors found for instance that longevity of irradiated insects, mice and rats was grater than 120% of unirradiated controls. Reproductive performance was found to be improved for most of the tested species. This was noted as increased number of young individuals and their size. At the same time their mortality rate decreased and sterility lowered. Appearance of those features was found to occur among others in insects, fish, chicken, mice, rats, dogs etc. exposed to low doses of ionizing radiation. Extensive list of references concerning this subject can be found in [1,4] .

Results of observations of living organisms published so far support existence of the hormesis phenomenon that is they confirm occurence of stimulation by appropriate doses of ionizing radiation. Radiation hormesis was not possible to be predicted from studies with high doses of radiation which led to decreased physiologic performance and death. Hormetic, low level doses cause accelerated development, increased resistance to disease and subsequent radiation, longevity and grater reproductive capacity.

Despite enormous number of studies where hormesis phenomenon was found its biochemical mechanism has not found satisfactory explanation so far. It is known that electromagnetic radiation when passing through absorbing medium loses its energy interacting mainly with electrons of atoms and molecules. This leads to appearence after about 10^{-12}s of excited molecules, ions, radicals and electrons. The paper by Kroh [19] discuss those problems in detail. In the cell both water and organic molecules (RH) are ionized:

$$H_2O \rightsquigarrow H_2O^{+} + e^{-}_{hydr} \quad \text{(hydrated electron, } H_2O^{-}\text{)}$$

$$RH \rightsquigarrow R^{+\bullet} \quad \text{(organic radical)} \quad + e^{-}$$

In the presence of molecular oxygen characteristic of tissues in the body, those processes lead to peroxidation:

$$e^{-}_{hydr} + O_2 \xrightarrow{k_1} O_2^{-\bullet} \quad \text{(superoxide radical)} \quad + H_2O$$

$$R\bullet + O_2 \xrightarrow{k_2} RO_2^{\bullet} \dashrightarrow ROOH \quad \text{(peroxide formation)}$$

With the rate constants $k_1 = 2 \times 10^{10}$ l $mol^{-1}s^{-1}$ and $k_2 = 10^7 - 10^9$ l $mol^{-1}s^{-1}$.

In the absence of O_2 and in presence of reducing agents e.g. sulfhydryl compounds (-SH), a chemical recovery takes place:

$$R\bullet + -SH \longrightarrow RH + -S\bullet$$

Ionization and certain recombination reactions e.g.:

$$R^{+\bullet} + e^{-} \longrightarrow R^{*}$$

$$RO_2^{\bullet} + RO_2 \longrightarrow ROH + RO^{*} + {}^1O_2^{*}$$

generate electronically excited species with their subsequent radiative relaxation in the form of low-intensity radioluminescence.

The atoms affected may be part of essential molecule such as DNA or a water molecule. Because of chemical composition of living organisms those reaction take place most often with water molecules. When energy from the affected molecule is transferred to another molecule, indirect action occurs causing in effect further ionization, free radicals formation etc. This energy transfer may take place in various ways and often excitations of collective character can act as mediators [24] .

Independently of whether this interaction is direct or indirect the final effect is similar: the functions of a cell are threatened by changes which have taken place in biologically important molecules. It is probable that when number of those processes overcomes its threshold value the organism becomes integrated to change metabolic priorities. Altered internal environment leads to changes of control mechanisms that show up in increased new mRNA, changed enzyme syntheses, membranes permeability and increased sensitivity to intercellural and environmental factors. Priorities are next reoriented for repair, for faster growth, accelerated development etc. Probability that mutation can play some role here is rather small since the effects appearing under influence of hormesis are seldom observed to occur in progeny of irradiated organisms.

5. Hormetic effects for man.

Man appears to be one of the most radiosensitive species. The magnitude of LD_{50}^{30} /see Tab.1./ for man equals to about 400R and this value is at least one order of magnitude smaller than the corresponding values for other living organisms. The limits of exposure for man are therefore more than adequate for other species. As it was already said realistically estimated total dose which a man is exposed to equals about 400 mR/year. Inhabitated regions are known to exist however where background ionizing radiation is much higher [20] . Some regions of Brasil belong to them in particular. First of all it is monasite beaches of Guarapari which provida up to 5 mR/h. Several thousands people in Espirito Santos state are exposed to radioactivity of 1R/year. Moreover those people consume food containing substantial amount of radioactive substances. No pathological signs of this radiation excess have been observed. Similar situation exist at Kerala coast of India where background radiation level of about 1300 mR/year have been reported. Food coming from those regions contains substantial amount of radium. Examination of inhabitans of Japan who survive the explosion of atomic bomb in 1945 shows that those people who receive doses of 11 to 120 R appear to live longer than those who receive either higher dose or none. There exists hypothesis that longevity of inhabitants of Caucasus or Himalaya mountains may be connected with relatively high intensity of cosmic radiation at high altitudes. There exist also rich epidemiological evidence showing that human cancer mortality rates are lower in areas of high natural background radiation than in low level radiation areas [1,4,5,6]. Analysis of variety of environmental factors, social standing and economic status revealed negative correlation between background radiation and death caused by cancer for US populations [5]. This has also been indicated in a report of the High Background Radiation Research Group, China [8].

Above data show that low, ecologically realistic doses of whole body irradiation may reduce cancer induction. Current radiation therapy of malignant deseases aims at direct destruction of malignant cells. Hormesis phenomenon appears in this respect as a possible new method of therapy. It is therefore extremely interesting and important to find out to what extent might the low-

-level radiation be beneficial to most individuals.
Theoretical models of the dose-response function existing so far cannot account for the negatively correlated association that have been observed between low levels of ionizing radiation and mortality rates of certain classification of cancer. Recently Hickey [6] has proposed a mathematical model which describes the shape of experimental dose-response curve i.e. when radiation hormesis at low-level exposure take place along with damaging effects of high-level radiation.

6. Ionizing radiation as a factor necessary for life.

Independently of the hormesis phenomenon of the ionizing radiation the question remains whether and to what extent ionizing radiation is indispensable for life.
We are all time plunged in the ionizing radiation coming from cosmic space and from local sources. This omnipresence of radiation suggests that it might played decisive role in formation of biologically important molecules and that presence of ionizing radiation might have been necessary condition for development of life.
Possible answer to the question whether radiation is essential for life is contained in a shape of the dose-response curve in region below ambient radiation that is in this part of the curve which lies to the left of the ordinate axis. If all ionizing radiation were harmful the curve should describe an increasing function with decreasing subambient dose. If radiation exhibited stimulation action only /i.e. hormesis phenomenon/ the slope of this curve in the corresponding range of doses should be equal zero. If the curve behaved as indicated in Fig.1.

by the dashed line it would mean that ionizing radiation is essential for some physiological function. Experiments performed by Luckey [1] and by Planel [21] indicate that radiation is essential for reproduction. Luckey cultivated Paramecium bursaria inside lead-lined containers. Shielded cultures displayed the reproduction rate about 10% of that of controls when thickness of the wall was 5cm and 5% when thickness was 10cm. The decreases were proportional to the thickness of the lead shielding. Comparable results based on Paramecium in a cave 200m underground have been reported by Planel's group. Intensity of cosmic radiation was reduced in this case 5-10 times with respect to its intensity at the ground level. In those conditions Paramecium showed only 47% as much reproduction as control. The same author has observed statistically significant decreased reproduction rates in protozoa incubated inside container with 10cm lead walls. He has compared his results with the control group incubated in normal conditions and with the irradiated controls inside lead container. Fig.3 illustrates results of that experiment. The average and one standard deviation is displayed. One can see that protozoa reproduced at slower rate when incubated in subambient radiation than controls incubated in ambient level. Experiments with Thorium to provide radiation equivalent to ambient give results equals to that of controls incubated in ambient radiation. Similar results were obtained with cloned sublines of Paramecium tetraurelia [10] . It has been found that in the case of Paramecium inside lead shielding cell fission occured at slower rates than for the controls. If however the same experiment was performed with ^{60}Co as a radiation source cell fission rate was accelerated.

Results of those few experiments show that radiation is essential for normal physiological function and life of living organisms. In this respect following Luckey [1,4] radiation hormesis should be understood as supplementation of an essential agent present in suboptimal quantities.

It seems to be urgent to perform similar experiments using representatives of other species of living organisms and also with the human cell cultures. In those experiments both exogenous and endogenous radiation should be reduced to few percent of ambient level and this should be done for several generations. To this aim the investigated organisms should be placed inside container which would ensure reduction of natural radiation background to 5% of its value. This would also require elimination of radioactive elements from a diet /first of all this would concern the isotope ^{40}K/ and also cleaning of air from radioactive, airborne particulates and gases. According to Luckey [4] under such conditions already the third generation of investigated organisms should exhibit very strong symptoms of radiation deficiency syndrome. It is expected that they manifest themselves in a form of abnormally low growth rate, slow physical and mental development, decreased fecundity, frangible health, poor utilization of food and decreased lifespan [4].

One of the most promising methodological approach to investigate hormesis phenomena and to elucidate their mechanisms seems to be radio-enhanced ultra low luminescence /biological chemiluminescence/. It has been well established that all living organisms from bacteria to man emit low-intensity radiation /1-10^4 $h\nu s^{-1}cm^{-2}$/ in the spectral range 180-1000 nm. This universal property of organisms is inherently associated with such fundamental processes as oxidative metabolism, cell division and death, detoxication and others. Parameters of this luminescence such as I, kinetic pattern I=f(t), spectral /energy/ and statistical /photon count frequency/ distributions are used as an integral indicator of the intactness and homeostasis of biological systems and fast non-invasive assays and diagnostic tools for the effect of external physical and chemical factors. Attempts to evaluate the absorbed very low doses of ionizing radiation have been undertaken [22] . For this purpose germinating seeds of the selected plant species have been irradiated with γ, β, γ, and neutrons various intensity and LET values. Very low doses within the hormetic range stimulated the intensity of ultra low luminescence slightly changing its kinetic pattern. These data indicate that hormetic doses of ionizing radiation prompt homeostasis of a living system to a higher level of the steady state metabolism[23]. Since the relative changes of ultra low luminescence parameters are well pronounced, i.e. the system: ionizing radiation-living organism-ultra low luminescence reveals synergic features, usually acting as an amplifier, these systems may be used as sensitive dosimeters for the evaluation of biological effects of low doses of ionizing radiation.

7. Summary and conclusions.

Taking into account results of reported experiments the traditional point of view that ionizing radiation is always harmful should be changed. The harmful effect on living organisms appears to take place not only in the case of excess of radiation but also in the case of its deficiency. This experimental fact based so far only on few but significant experiments implies the question concerning optimum background radiation level that would be beneficial to most individuals. There exist now extensive evidence concerning plants and animals that this level is slighty higher than the normal background radiation. Precisely at this level that is called low-level dose stimulating effect take place. Extensive studies of this phenomenon have focused mainly upon practical applications. They provide also information concerning safety limits for living organisms exposure indicated by ZEP that is the highest dose that gives results equivalent to ambient radiation.

Data concerning reaction of human organisms on low-level dose come mainly from epidemiological studies of populations inhabitating regions having different level of background radiation. Negative correlation between background radiation level and death attributed to cancer has been found. This may mean that low doses of whole body irradiation, this is hormesis with ionizing radiation for human idividuals may provide a new kind of therapy in case of cancer related desease.

The data gathered so far suggest that hormesis phenomenon may be regarded as a law of nature but as far as its wide application is concerned more data is certainly needed.

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Figure captions:

Fig.1. A hypothetic dose-response curve. Explanations in the text.

Fig.2. Increased yield from irradiated plants.

Fig.3. Increased growth rates in irradiated mice.

Fig.4. Protozoa's reproduction rates for different radiation levels. Explanation in the text.

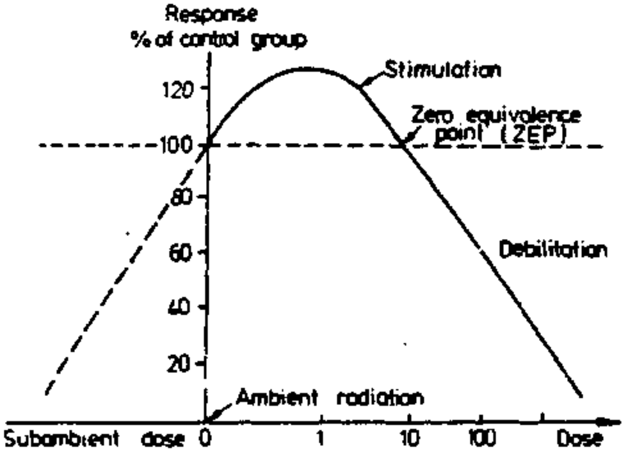
Response
% of control group
120
100
80
60
40
20
Stimulation
Zero equivalence point (ZEP)
Debilitation
Ambient radiation
Subambient dose
0
1
10
100
Dose

Fig. 1

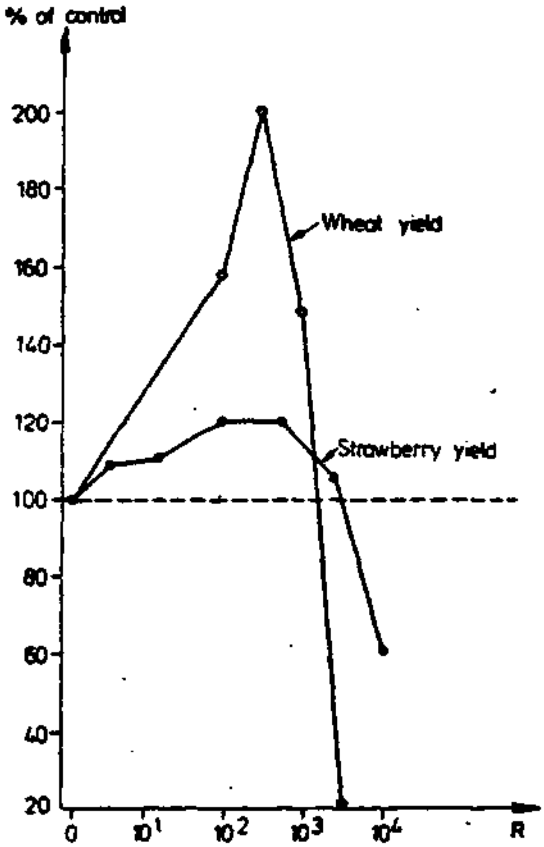
% of control
200
180
160
140
120
100
80
60
40
20
Wheat yield
Strawberry yield
0
10^1
10^2
10^3
10^4
R

Fig. 2

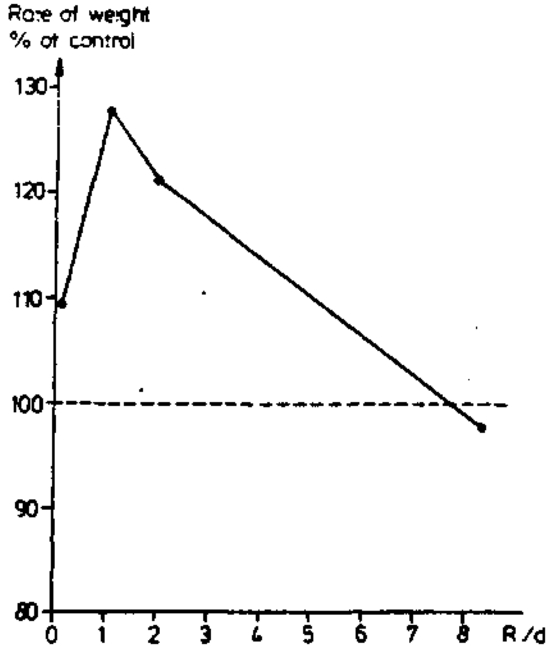
Rate of weight
% of control
130
120
110
100
90
80
0
1
2
3
4
5
6
7
8
R/d

Fig. 3

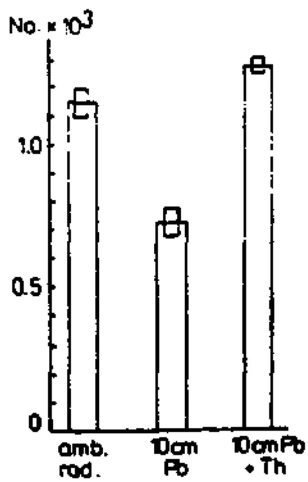
No. × 10³
1.0
0.5
0
amb. rad.
10cm Pb
10cm Pb + Th

Fig. 4