THE TOXICOLOGY OF RADIOACTIVE SUBSTANCES

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VOLUME 2

Radioactive Cobalt, Sodium Phosphorus and Gold

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PREFATORY NOTE

THIS collection contains results of investigations on the chronic effects of radioactive cobalt on the body and the effects of intratracheal injection of soluble radioactive sodium chloride and insoluble compounds of radioactive phosphorus and gold.

Data are presented on the metabolism of radioactive cobalt after single and chronic internal administration and the resultant tissue doses.

The papers included in the collection are devoted to the effect of radioactive cobalt on the hemopoietic system, certain aspects of metabolism (protein and carbohydrate), changes in the cardiovascular system, pathomorphological shifts in the organs and the stimulation of excretion of radioactive isotopes from the body. On the basis of the results of the chronic experiment maximum permissible concentrations of radioactive cobalt in water are proposed.

The difference in effect of soluble and insoluble compounds of radioisotopes (sodium, phosphorus and gold), and the occurrence of growths in the lungs after intratracheal njection of insoluble compounds of radioactive phosphorus and gold are established. Tissue doses resulting in blastomogenic growth are calculated.

This collection is intended for those working in the fields of radiobiology and radiohygiene, doctors in medical departments and epidemiological hospitals, physicists and others concerned with the establishment of maximum permissible doses of radioisotopes.

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INTRODUCTION

FURTHER RESEARCH ON THE TOXICOLOGY OF RADIOACTIVE SUBSTANCES

E. B. KURLYANDSKAYA

FOR a number of years workers in the Radiotoxicology Laboratory of the Institute of Hygiene, Work and Occupational Diseases, Academy of Medical Sciences, U.S.S.R. have been studying the toxicology of radioactive substances. The main task of these investigations has been a study of their characteristic behaviour in the body and particularly their long-term effects, since this aspect may be important in the peaceful uses of ionizing radiation.

The experimental results obtained will aid the explanation of the pathogenesis of sickness resulting from the constant intake by the body of small quantities of radioactive matter and its earlier diagnosis. This is especially important since the chemical, physical and biological properties of radioactive substances, in particular those whose stable isotopes are microelements, may join with the radiation emitted to produce a combined effect. Our experimental results confirm that the early symptoms of the effect of different radioisotopes may vary as a result of this.

Problems concerning the long-term consequences of internal administration of soluble and insoluble radioactive compounds, their effect on pregnancy and offspring and the search for means of stimulating excretion of radioisotopes have an important place in our investigations. The results obtained may serve as a basis for a biological evaluation of maximum permissible concentrations of radioisotopes.

Earlier work has been published in the collection *The Toxicology of Radioactive Substances*, Vol. I, which dealt with radioactive strontium, caesium, ruthenium and radon.

The material in the present collection represents a logical development of the Laboratory's work on the chronic effects of radioisotopes and concerns mainly the toxicology of radioactive cobalt (^{60}Co).

This isotope was chosen because of its widespread application. It is not only used as a source of external radiation but is also widely used in scientific investigations and as a control for technological processes

in industry both in powder and solution form. It can also be added to metal in the smelting process, appear in the form of an aerosol when turning radioactive metal, and so on. The cheapness and ease of production of ^{60}Co will probably extend its application still further.

However, the physical and chemical properties of this radioisotope, its long life and the properties of its stable isotope as a microelement constrain us to approach its further application with great caution and make still more important the study of its biological effects, especially the chronic effect of small doses.

A brief description of the physical and chemical characteristics of ^{60}Co must be given.

^{60}Co has a half-life of 5.3 years. It emits β-particles (maximum energy 0.3178 MeV) and successively 2 γ quanta with energies of 1.17 and 1.33 MeV.

The stable isotope of cobalt is widely found in nature. According to A. E. Fersman the content by weight of cobalt in the earth's crust is 2×10^{-3} per cent.

The presence of cobalt in plants and animals was discovered in 1922 by Academician V. I. Vernadskii. Subsequently the physiological role of cobalt has been established by numerous investigators. It is contained in the organic complex of vitamin B_{12} and is a microelement which participates in hemopoiesis, stimulating erythropoiesis. This property of stable cobalt makes the study of the biological effects of its radioactive isotope particularly interesting, when considering the effect of ionizing radiation on the hemopoietic processes.

This collection represents the results of 2 years of experimental work by the Radiotoxicology Laboratory of the Institute of Hygiene, Work and Occupational Diseases, Academy of Medical Sciences U.S.S.R. on the chronic effects of ^{60}Co on rats and rabbits.

The main experiment was carried out on rabbits. In total, five groups of animals were included in the chronic experiment (continuing for 2 years). The first group of 10 rabbits received $^{60}CoCl_2$ in a daily dose of 1.25 μc/kg weight. The second group of 13 rabbits received 12.5 μc/kg of $^{60}CoCl_2$ daily. The third control group of 5 rabbits received daily 1.9 γ of stable cobalt, corresponding to the quantity of cobalt (calculated for the metal) given to the rabbits of the first group. The fourth group (5 rabbits) was a control for the second group and received 19 γ of stable cobalt daily. The fifth group of 10 rabbits served as a biological control.

A sixth group of rabbits, which received for 2 months a large dose of ^{60}Co, 65 μc/kg (87 γ stable cobalt), was included in the experiment for particular tests (dosimetrical, biochemical, etc.). The pH of the $^{60}CoCl_2$ solution was brought close to neutral.

The quantity of ^{60}Co—1.25 and 12.5 μc/kg of body weight—exceeded the maximum permissible concentration for water, proposed by Morgan, by 100 and 1000 times.*

Systematic observation was maintained on the animals' general condition and the following factors were studied:

(1) absorption, excretion and distribution of ^{60}Co at different periods during administration and determination of tissue doses;
(2) the state of the hemopoietic system (peripheral blood and bone marrow by intra-vitam puncture) with application of functional stresses (bleeding, parturition);
(3) capillary permeability of eyes and skin;
(4) electrocardiographic changes during the intoxication period of administration and also during application of functional stresses (Aschner's test, olfactory-cardiac reflex with inhalation of ammonia, pharmacological tests);
(5) certain aspects of protein metabolism (total protein, its separate fractions, residual nitrogen);
(6) certain aspects of carbohydrate metabolism (blood sugar, glycogen content and its ease of breakdown by β-amylase, activity of phosphorylase and hepatal amylase);
(7) morphological changes;
(8) methods for stimulating excretion of ^{60}Co from the body;
(9) the long-term effects of both ^{60}Co and intratracheal injection of ^{24}Na, ^{32}P in the form of chromium phosphate and colloidal ^{100}Au.

All the main tests were carried out on all the animals at the same time intervals. Firstly it was interesting to determine the distribution of ^{60}Co in rats and rabbits resulting from a single administration by different routes (oral and subcutaneous) and to evaluate from the data obtained the amount of β- and γ-radiation present in the animals. The results obtained are presented in the paper by G. A. Abrunina, "^{60}Co Metabolism in Rats and Rabbits after Single Administration and Calculation of the Body Dose". The author has established that after both oral and subcutaneous administration of $^{60}CoCl_2$ the greatest radioactivity is found during the first 1–3 hr, after which ^{60}Co is rapidly excreted from the body. In rats during the first 7 days after subcutaneous injection 77 per cent of ^{60}Co is excreted in the urine and 10 per cent in the feces. The corresponding figures for rabbits are 84 per cent in the urine and 5 per cent in the feces. After oral administration in rats 13 per cent of the administered dose is excreted in the urine and 80 per cent in the feces. In rabbits the correspond-

* Recommendations of the International Commission on Radiological Protection, *Brit. J. Radiol.* No. 6, 1955.

ing figures are 11 and 54 per cent. In rats from 17 to 33 per cent of administered ^{60}Co is absorbed from the gastro-intestinal tract; in rabbits—from 13 to 30 per cent.

The highest specific activity by both means of administration is found in the liver, kidneys, suprarenals and pancreas. The skeletal muscles, nervous system and bones exhibit low specific activity. The results obtained somewhat contradict those of foreign writers who have considered the spleen to be the second critical organ, whereas according to G. A. Abrunina's results the kidneys exhibit the second highest specific activity. A relationship was found between the quantity administered and the average amount of radioactivity in the body of animals which can be expressed by the equation:

$$A = ad^b$$

where A is activity found in the body, d—daily amount administered and a and b are constants, $b < 1$.

Study of the accumulation and excretion of ^{60}Co in rabbits and rats during daily oral administration over 2 years (G. A. Abrunina—*Accumulation and Excretion of* ^{60}Co *in Animals and Tissue Doses during Daily Oral Administration*) disclosed characteristics similar to those earlier established by E. B. Kurlyandskaya and A. A. Rubanovskaya for ^{89}Sr and ^{134}Cs. It was found that during chronic administration of $^{60}CoCl_2$ an equilibrium is rapidly established (from 2 weeks to 1–2 months) between the administered and excreted quantities of ^{60}Co. Consequently, the radioactivity of all animals which died at intervals between 2 and 22 months was very similar. A level of radiation dose has also been established.* Thus the daily β-radiation dose for a daily oral administration of 1.25 μc/kg of ^{60}Co is 0.10 rep to the liver and 0.084 rep to the kidneys. With administration of 12.5 μc/kg of ^{60}Co to rabbits, the daily dose is 0.61 rep to the liver and 0.29 rep to the kidneys. The corresponding average doses of γ-radiation to the body for the same administered dose were 0.24–1.16 r per day and for the abdominal cavity—0.57–3.30 r per day. The data obtained show that the radiation dose in the body cannot be calculated from the activity administered. Administration of the same activity can lead to different ionizing doses depending on the character and course of distribution of the isotope. The behaviour of the isotope in the body depends on its chemical properties, the form in which it is administered, the ratio of stable to radioactive isotope in the preparation and on other biological, physical

* The present collection of papers was at the printers when the publication GOST 8848–58, 1st Jan. 1959, expressing absorbed radiation dose in rads was issued. The units used here are the roentgen for X-and γ-radiation and the rep for β-radiation. Expressed in rads, these values would be 10–15 per cent higher.

and chemical factors. This is illustrated by the papers of G. A. Abrunina and T. A. Kochetkova and G. A. Abrunina. Thus, for example, if the ^{60}Co daily dose administered to rabbits in the chronic experiment is calculated in microcuries then these doses exceed the maximum permissible concentrations for water as proposed by Morgan by 100 and 1000 times. According to the calculation the doses of internal radiation would also exceed the maximum permissible by 100 and 1000 times. In fact it appears that the average radiation dose in the body after administration of 1.25 μc/kg ^{60}Co exceeds the generally accepted maximum permissible (0.05 r) by only 5 times, and in the "critical" organ—the liver*—by 14 times. With administration of 10 times the amount of ^{60}Co (12.5 μc/kg) the average radiation dose in the body is raised by 25, and in the "critical" organ—by 80 times. Consequently, to establish the true radiation dose in the body study of the isotope's behaviour is needed, as the radiation dose in a tissue is proportional to the radioactivity of that tissue and only in relationship to this dose can its biological effectiveness be evaluated.

Similarly chronic radiation sickness develops in rabbits which have received daily a quantity of ^{60}Co sufficient to create an average γ-radiation dose for the whole body of 0.24 and 1.16 r per day (in total during 18–24 months the animals of the first group received 135–185 r and the second group during $7\frac{1}{2}$–24 months—250–825 r).

During the first 4 months of observation the increase in weight of the animals of the first (1.25 μc/kg) and second (12.5 μc/kg) groups was somewhat higher than that of the control animals. Subsequently the weight of the experimental animals did not differ from that of the controls. A significant loss of weight before death was observed in the experimental animals.

Two weeks after commencement of ^{60}Co administration to rabbits in a dose of 12.5 μc/kg changes in erythrocyte count occurred in the form of an increase of 1.5–2 millions (N. L. Beloborodova—*Changes in Hemopoiesis during Prolonged Internal Administration of* ^{60}Co). This increase took place without the reticulocytosis which was observed by N. L. Beloborodova during chronic administration of ^{134}Cs, ^{89}Sr and ^{106}Ru. Hemoglobin and colour index were also increased by 30–40 per cent. After 15 months a decrease of 25–28 per cent occurred in the erythrocyte number, which was scarcely reflected in the reticulocyte number. It should be noted that with the smaller doses of ^{60}Co (1.25 μc/kg) the decrease in the erythrocyte number was accompanied by an increase in the number of reticulo-

* For the "critical" organ—the liver—Abrunina took the dose of γ-radiation as calculated for the abdominal cavity, which is higher than the average for the whole body. The β-radiation dose in the organ was also calculated.

cytes up to the upper limits of normal (up to $45^0/_{00}$), but that with a dose of 12.5 μc/kg the number remained at $20–25^0/_{00}$.

Thus changes in erythropoiesis differed from those observed by us with administration of other isotopes. We connect this with the specific effect of cobalt as a microelement participating in the hemopoietic processes. It must be noted that an equal weight of stable cobalt did not produce similar effects. It is possible that these effects were the result of the combined action of cobalt as a microelement and its radioactivity on the functioning of the hemopoietic organs.

The impairment of leukopoiesis was slight in rabbits which received 1.25 μc/kg ^{60}Co but much more pronounced with a dose of 12.5 μc/kg. In rabbits receiving the larger dose a gradual decline in the general leukocyte number to 4900 (as against 9000 in the control animals) was observed after the ninth month.

Changes in lymphopoiesis in the animals of the first group (1.25 μc/kg) took the form of lymphocytosis. This was also observed by us after administration of other isotopes. In the rabbits of the second group (12.5 μc/kg) a gradual but constant decline of the relative and absolute lymphocyte numbers began in the first month of administration. This may be explained either by a decline in the formative capacities of the spleen as a result of the destruction of lymphoid tissue which occurred in a series of rabbits, or by a retardation of lymphocyte maturation. The possibility of a shortening of the life-span of lymphocytes in the peripheral blood as a consequence of constant prolonged irradiation is not excluded.

The defectiveness of the hemopoietic system was especially evident in parturition and blood loss. On the first and following 3–4 days after parturition acute reticulopenia was observed in all females. In the majority prolonged post-partum anemia developed. These changes were noticed at later periods during ^{134}Cs and ^{89}Sr administration. We were unable to study post-partum blood changes at a later stage of administration (16–20 months) because pregnancy either failed to occur or terminated.

After loss of blood (1 per cent by body weight of blood was removed) reticulocytosis of up to $70^0/_{00}$ occurred in the control rabbits after the first day but only towards the 8th day in those receiving ^{60}Co.

Leukocytosis was observed in the control animals in the first days after blood loss, but in the experimental animals only on the 8–9th day, chiefly because of an increase in the number of neutrophils.

Progressive observation of the morphological composition of the bone marrow disclosed an abnormality in the red branch. In the 14th month of administration an enlargement of the red branch was detected in 50 per cent of rabbits receiving 12.5 μc/kg ^{60}Co (1.16 r per day), preceding and then accompanied by developing hyporegenerative anemia.

After 20–22 months this enlargement of the red branch was observed in all the animals of this group.

Attention is drawn to the acute decrease of the number of monocytes and lymphocytes in the bone marrow, indicating profound changes in the reticulo-endothelial and lymphoid tissues. These observations are confirmed by the picture of changes in the spleen. In contact preparations of the spleen of these rabbits an average 20 per cent fall in the general lymphocyte number was observed and a relative increase of prolymphocytes and large lymphocytes giving evidence of a retardation of lymphocyte maturation. Possibly this factor is the cause of the developing lymphopenia. These same preparations disclosed foci of ectopic myeloid hemopoiesis (up to 21 per cent neutrophils) not normally found.

Observation of the morphological composition of the bone marrow after bleeding showed a sharp shift in the red branch. Thus, in the control animals after bleeding, an increase of more than 50 per cent occurred, chiefly in the form of polychromatophilic erythroblasts and young cells and by the 9th day the red branch had become entirely normal. In the experimental animals activation of the red branch of the bone marrow was absent on the 4th day and began on the 9th solely on account of polychromatophilic normoblasts. The number of young cells fell. This retardation of the reaction of the bone marrow in the experimental animals was accompanied by impairment of the maturation processes, which was reflected in the peripheral blood by the extremely slow growth of the reticulocyte number after bleeding.

The changes in lymphopoiesis after bleeding are of interest. Whereas in the control animals in the first days after bleeding lymphocytosis was observed, in the experimental animals the number of lymphocytes fell to 1500–2000 per mm^3.

The absence of gross pathomorphological changes in the bone marrow (T. A. Kochetkova, A. S. Kaplanskii), and the slow restoration of the erythrocyte and leukocyte numbers after bleeding are evidence of functional changes in hemopoiesis and the preservation of compensatory mechanisms after chronic (up to 16 months) administration of ^{60}Co.

Changes in the hemopoietic system were also found in the offspring of rats to which ^{60}Co had been administered orally in a daily dose of 150 μc/kg weight before and during pregnancy and after parturition. Here the γ-radiation dose in the body was established at a level of about 1 rep per day, i.e. it was close to that found in rabbits by daily administration of a much smaller quantity of ^{60}Co (12.5 μc/kg). This supports what has been said above concerning the part played by biological factors in the evaluation of ionizing doses, in this case the specific species characteristics of the animals.

N. L. Beloborodova, E. K. Red'kina and V. L. Viktorova have shown that in the offspring of rats which have received ^{60}Co impairment of erythropoiesis occurs, particularly pronounced in the spleen where progressive "active" hyperplasia of the erythroblastic tissue arose. There were no important changes in white blood formation.

In rabbits receiving 12.5 $\mu c/kg$ ^{60}Co changes appeared after 2 months in the albumin–globulin ratio in the blood serum, namely a lowering of the albumin–globulin coefficient chiefly due to an increase of the globulin fraction (E. D. Grishchenko). This latter was accompanied sometimes by a lowering of the absolute albumin level, but more often by an increase of the general protein content. This disproportion in the protein composition of the serum lasted 7–9 months, after which the normal ratio of the above mentioned protein fractions and the protein content were re-established. Subsequently the normal albumin–globulin coefficient was maintained but protein content again increased. A similar picture was obtained with rabbits receiving the smaller dose (1.25 $\mu c/kg$) with this difference only, that disruption of the albumin–globulin balance extended over a somewhat longer period (up to 10 months). Irreversible changes in the protein complement of the blood serum in the animals under test usually occurred before death. After 15–20 months electrophoretic examination of proteins showed an increase of globulins, chiefly of γ-globulin.

It is interesting to note that changes in the A/G ratio occur after bleeding, which is evidence of a weakening of the systems which synthesize albumins.

Thus, changes in the protein fractions arose at an early phase of chronic radiation damage. Then, at 8–9 months, the ratio of the protein fractions returned to normal, being again disrupted after 14–17 months. The final period (21–23 months after commencement of administration of ^{60}Co) is characterized by pronounced changes of the protein fractions, chiefly of γ-globulins, and the immunobiological resistance of the animals declines. This is corroborated morphologically by tissue microbism of organs and also by the death of the majority of the animals from secondary infections.

In rabbits receiving a daily dose of 1.25 and 12.5 $\mu c/kg$ of ^{60}Co a steady tendency to lowering of the blood sugar level was detected. At this period the sugar curves, taken after loading with glucose, display a clearly hypoglycemic character. By the 18th month of administration the sugar level before and after loading with glucose is normal. By the 21st–23rd month, significant hyperglycemia develops. This, as determination of the glycogenolytic activity of water-soluble liver extracts showed, develops as a result of direct damage to the enzyme systems of this organ. The phosphorylase is the first to suffer.

Glycogen structure is significantly changed. Whereas with a liver dose of β- and γ-radiation of approximately 0.7 rep per day for 21–23 months the breakdown of glycogen by β-amylase remains normal over this period, with a dose of 3.3 rep per day (12.5 μc/kg) it is 25 per cent, and with a dose of 11.4 rep 6 per cent, as against 42–47 per cent in the control. Glycogen content of the liver is unchanged. Thus the synthesizing capacity of the liver in relation to glycogen begins to be impaired only at a liver dose of 3.3 rep (in the conditions of our experiment with a general body dose of 1.16 r per day). This is demonstrated by the fact that the liver begins to form glycogen with shortened side chains, and also by the changes of the sugar curves after loading with glucose, as shown in the work of N. I. Vinogradova and Ye. D. Grishchenko (*Impairment of Some Aspects of Carbohydrate-Phosphorus Metabolism in Rabbits after Prolonged Administration of* ^{60}Co), and also of N. I. Vinogradova (*The Effect of* ^{60}Co *on Carbohydrate Metabolism in Rat Liver*).

Changes in capillary permeability of the eye, determined by penetration of fluorescein in the aqueous humour of the anterior chamber and by its protein content were detected in the 7th–9th months of ^{60}Co administration of 12.5 μc/kg. After 9–11 months capillary permeability for fluorescein in the eye increased in the majority of the experimental animals. Protein content of the aqueous humour also increases at this period. Subsequently, some decrease of capillary permeability occurs, but is does not return to normal throughout 19$\frac{1}{2}$ months of observation. A tendency towards a change of cutaneous permeability was detected only at the 9th–11th months and took the form of an increase in the number of cases with a large area of stain diffusion in the ^{60}Co group of rabbits compared with the control (A. A. Rubanovskaya—*Changes in Capillary Permeability of Eyes and Skin of Rabbits during Chronic Internal Administration of* ^{60}Co).

Thus, changes in capillary permeability occur with large dosage and at a later period than do changes in the morphological composition of the blood and in protein metabolism. This indicates, presumably, the secondary character of these changes, developing against a background of pronounced trophic impairments.

At the 7th month of administration in rabbits fluctuations of all waves of the electrocardiogram were found, largely in the form of an increase mainly of the *QRS* complex in the thoracic, but also frequently in standard leads. Changes in voltage height of the electrocardiogram bore a phasic character: at 7–8 months the *P* and *T* waves increased more than twice, at 12–13 months voltage was normal and at 18–20 months decreased.

Pronounced changes were noticed in the terminal part of the ventricular complex, mainly of the *T* wave. In the last period of administration gradual lowering takes place, and subsequently in some rabbits

inversion of the *T* wave. In some rabbits receiving the low ^{60}Co dose (1.25 μc/kg per day) the electrocardiogram returned to normal, in others not. The normalization of the terminal part of the ventricular complex in certain rabbits is evidence that the changes of the myocardium in our experimental conditions are functional rather than organic (*Electrocardiographic Investigations of Rabbits during Prolonged Internal Administration of Small Doses of Stable and Radioactive Cobalt*—A. O. Saitanov). This is confirmed by the histological investigation of the cardiac muscles carried out by A. S. Kaplanskii. No large-scale structural lesions of the cardiac muscle were discovered in the majority of rabbits. Only lesions connected with general changes of blood vessels were noticed.

The use of functional tests (Aschner's test, the olfactory-cardiac reflex during ammonia inhalation, adrenaline injection) disclosed certain changes in the heart's electrical activity apparently connected with the impairment of nervous regulation. Thus, an increase of excitability of the vagus nerve and a raising of the threshold of sensitivity to adrenaline were detected in the experimental animals by contrast with the controls (*The Electrocardiogram of Rabbits during Functional Tests (Aschner's test, ammonia inhalation and adrenaline injection) in conditions of Chronic Administration of Small Doses of* ^{60}Co—I. N. Golovshchikova). The importance of the so-called functional stresses, enabling the detection of changes in the nervous regulation of the heart and other systems, must be emphasized.

Pathomorphological analysis (*Morphological Changes in Rabbits during Chronic Internal Administration of* ^{60}Co—A. S. Kaplanskii) of the organs of experimental animals disclosed significant pathological changes in animals dying at various intervals after administration. The following were detected: pronounced changes of the hemopoietic organs; proliferation of cells of the reticulo-endothelial system in different organs; so-called specific pneumonias; atrophic and sclerotic lesions of the mucous membrane of the gastro-intestinal tract; dystrophic and sometimes also necrobiotic lesions of the liver, diffuse interstitial focal sclerosis of the liver; lesions of the urinary bladder epithelium, dystrophic and atrophic lesions of the gonads and hemosiderosis of internal organs. These lesions were very pronounced in rabbits which received 12.5 μc/kg of ^{60}Co and to a lesser degree at the dose of 1.25 μc/kg.

In certain females, intrauterine fetal death and development of tumours at different foci were observed. The extent of these occurrences was dependent upon dose and individual sensitivity of the animal.

Thus, these investigations have demonstrated the particular characteristics of the radiotoxic effects of ^{60}Co by comparison with other isotopes. The order of development of each pathological process was established.

Thus, it has been shown that changes in the hemopoietic system and in the ratio of the serous protein fractions in rabbits undergoing chronic ^{60}Co administration arise considerably earlier and with smaller doses than changes in carbohydrate metabolism, the bioelectrical properties of the heart and the capillary permeability of the eyes and skin. Obvious changes in nervous regulation of the heart also occur against the background of already pronounced biochemical changes.

The investigations also disclosed effects of ^{60}Co on the body similar to those of other isotopes studied earlier. Thus, in published material on the biological effects of ^{134}Cs, ^{106}Ru and ^{89}Sr we indicated the existence of stages in the development of the pathological process during chronic administration of these isotopes to rabbits (cf. the collection: *The Toxicology of Radioactive Substances*, Vol. 1, 1957). We had grounds for speaking of three stages of which the first stage was characterized by a state of stimulation and lability of the hemopoietic system. During this period more or less sharp fluctuations of the numbers of reticulocytes and thrombocytes, the total number of leukocytes and their separate forms, etc. were observed. In the second stage some stabilization of the majority of blood factors at the initial level occurred (11–20 months after commencement of administration). In the third stage a distinct weakening of the hemopoietic function was observed. M. S. Lapteva-Popova, studying the effect of small doses of external γ-radiation on the hemopoietic system in the chronic experiment, has detected four successive stages in the development of chronic radiation sickness: the first stage—primary reaction, second stage—depression, third stage—compensation, and fourth stage—terminal. In our experimental conditions we were unable to distinguish the second stage—depression, which occurs in M. S. Lapteva-Popova's investigations before the compensation stage.

Study of the course of development of chronic radiation sickness during daily oral administration of $^{60}CoCl_2$ for 2 years again disclosed the same three stages of development, more clearly marked with a low ^{60}Co dose and effaced with larger doses (12.5 μc/kg).

These stages may not coincide in the different systems. Thus, the compensatory stage for the blood and serous protein systems occurs considerably earlier than for the bioelectrical activity of the heart, carbohydrate metabolism, etc.

The analysis of extensive experimental results has shown that during oral administration of ^{60}Co in doses exceeding the maximum permissible for water (according to Morgan) by 100 and 1000 times pathological changes develop in the body. When it is realized that with a quantity of ^{60}Co 100 times in excess of Morgan's maximum permissible, the average dose of general γ-radiation to the rabbit's body exceeds the generally