EFFECTS OF IONIZING RADIATION ON THE DIGESTIVE SYSTEM

by

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To the fond memory of my teacher

Academician Konstantin Mikhailovich Bykov

Note

This book has been written for the general use of physicians and scientists. It deals with an urgent problem in modern medicine and contains a vast amount of varied experimental material on changes in the functions of the digestive organs caused by ionizing radiation, together with an analysis of the mechanism of these changes. Several ways of preventing and treating serious disorders of the digestive organs during radiation sickness are outlined.

Foreword

Physiologists, pathologists, and clinical physicians were first confronted with the problem of radiation lesions of the digestive organs fifteen years ago as a result of the widespread use of atomic energy in various branches of the national economy. It has now become one of the most pressing problems of modern medicine, justifying the intensive experimental work of Soviet and foreign investigators in the field.

For the past eight years, a team of scientists under my direction has been studying in detail; 1) radiation-induced impairment of the secretory function of the salivary glands, stomach, pancreas, liver, and small intestine, 2) motility of the gastrointestinal tract, 3) the structure of the various digestive glands, and 4) certain aspects of the neurohumoral mechanisms regulating digestive functions.

This research has been conducted in conformity with the general theory of I. P. Pavlov on higher nervous activity and the teaching of K. M. Bykov on functional interrelations between the cerebral cortex and the internal organs. Consequently, with respect to method and experimental techniques, it differs radically from a good deal of the work on radiation injury to the digestive organs done by many investigators, particularly those in foreign countries.

The availability of our own experimental data, derived from prolonged chronic experiments on 100 dogs, and the lack of surveys and monographs on radiation injury to the digestive system in world literature encouraged us to systematize our findings and compare them with those of other authors. As soon as we started this work, however, we encountered difficulties familiar to all investigators who have assumed a task of this kind. One can compare and contrast only results obtained on the same animals under identical experimental conditions. The literature contains information on radiation lesions of the digestive tract in man and in a great variety of animals—dogs, cats, rabbits, rats, mice, frogs, pigs, and monkeys—all of which have varying degrees of resistance. Moreover, observations were sometimes made during acute experiments, with all the shortcomings inherent in this type of investigation; sometimes during chronic experiments with "fistula" animals; and sometimes on human patients.

Different authors have used different doses of irradiation, the limits of which have ranged from the maximal permissible dose to

several thousand roentgens. Neither the technical conditions of the irradiation nor the dose rate, was found to be constant; hence, the animals' radiation sickness differed in severity and outcome, despite the apparent uniformity of the dose. Furthermore, sometimes total-body external irradiation, chiefly X-rays, was used; at other times, internal irradiation with a variety of radioactive substances of unequal power was used: phosphorus, polonium, strontium, nuclear fission products of uranium, etc. A number of investigators studied functional changes in the digestive organs after external local irradiation with gamma and beta rays, again with different dosages, dose rates, and experimental conditions (acute and chronic).

These authors studied the digestive functions without taking into account the functional state of the higher divisions of the central nervous system and the typological characteristics of higher nervous activity which, in our opinion, largely determine the individual radiosensitivity of the organism and substantially influence the course and outcome of radiation sickness. These investigators often concentrated on changes in the digestive functions while ignoring the general condition of the organism, the clinical picture of the disease, or the stage of development of the pathological process.

Therefore, in systematizing and generalizing these data, we were compelled to rely chiefly on our own factual material. First of all, our data was collected in a single consistent research effort. Secondly, they were obtained by uniform experimental methods. Thirdly, the experiments were on the same kind of animals (dogs) kept under similar conditions of laboratory life and diet. Fourthly, they all pertained to total-body X-irradiation with an RUM-3 apparatus using the same doses (250-350 r) and dose rates. Finally, we took into account, on one hand, the functional state of the higher divisions of the brain (as determined by conditioned salivary reflexes), and the typological characteristics of the animals' higher nervous activity (established by means of the "lesser standard" tests), and, on the other, the activity of the digestive organs (studied by chronic fistulas).

Our data then had to be compared with the clinical picture of radiation sickness. Accordingly, in all investigations of digestive functions, we simultaneously determined peripheral blood changes (leukocyte and erythrocyte counts, hemoglobin content, erythrocyte sedimentation rate), body temperature and weight, food excitability, motor activity, and other indicators of pathological conditions.

It is not for us to judge how successful we have been in our attempt to organize our material and interpret it in the light of modern radiobiology, radiophysiology, and radiopathology. We shall be satisfied if this work helps in promoting further research on the problem, assists clinicians and other physicians in understanding the physiological mechanisms responsible for the development of

radiation injury to the digestive organs, and aids in the search for new and more effective methods of preventing and treating radiation sickness. We shall be extremely happy if our modest effort contributes to the advance of Soviet science.

In conclusion, I should like to express my sincere thanks to my esteemed co-workers M. E. Vasilenko, S. V. Voĭnov, A. D. Golovskiĭ, G. Dzhagiik, V. B. Zakharzhevskiĭ, V. N. Zvorykin, A. E. Karpenko, A. G. Korobkina, A. G. Kuzovkov, É. K. Kuznetsova, N. A. Lapshin, A. V. Myasnikov, E. V. Pashkovskiĭ, A. V. Popov, V. L. Popkov, M. S. Seregin, P. V. Simonov, A. A. Fadeeva, Hua Kuan, I. G. Chursin, and N. A. Yaroslavtseva, who took an active part in working out the problem of radiation lesions of the digestive system, and to the technicians who took good care of the surgical and sick animals and were unfailingly helpful in carrying out the physiological observations.

Professor I. T. Kurtsin

May 13, 1959
Leningrad

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PART II

MECHANISMS OF IMPAIRMENT OF THE ACTIVITY OF THE DIGESTIVE ORGANS DURING RADIATION SICKNESS

Introduction

Radiation sickness as an independent human disease has become the object of earnest attention by physicians and clinicians comparatively recently.

Isolated cases of radiation lesions turned up soon after Roentgen discovered X-rays in 1895 and A. Becquerel and M. and P. Curie observed in 1896 that certain substances (compounds of uranium, radium, polonium, chalcocite, autunite) were naturally radioactive. A year after the discovery of X-rays, Becquerel and P. Curie found burns on their hands caused by radium rays. The first case of radiation sickness was described six years later. There were 7 such cases in 1907, 31 in 1908, and 54 in 1911. Later, the incidence of radiation injuries increased considerably following Rutherford's discovery of artificial nuclear fission and Frederick and Irene Joliot-Curie's discovery of how to obtain radioactive substances artificially.*

Nine deaths were recorded between 1922 and 1924 among workers painting watch dials with paints containing radioactive substances. In 1929 Martland described 18 fatalities due to injury by ionizing radiation, and the press published 126 more such cases the next year. Cases of skin cancer and serious blood diseases (leukemia) were observed in roentgenologists and radiologists exposed to external irradiation by roentgen and gamma rays in the course of their work. Lung cancer was found in Yakhimov and Schneeberg miners working in an atmosphere with high concentrations of the radioactive gas radon.**

The extensive use of atomic energy nowadays in various branches of the national economy, technology, and science—biology, physiology, and medicine in particular—has made radiation injury an urgent problem attracting the attention not only of specialists in a variety of clinical disciplines, but also of a vast army of theoretical scientists, from physicists and chemists in various specialties to biologists, physiologists, pharmacologists, histologists, and pathologists.

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*See Marie Curie. Radioactivity. OGIZ, Gostekhizdat, 1947, pp. 328, 343.

**The Danger of Ionizing Radiation to Man. Izd. IL, Moscow, 1958, p. 27.

Among the numerous problems pertaining to the biological effects of ionizing radiation, which have been thoroughly investigated in recent years in many countries of the world, radiation injury to the digestive system occupies a special place. The reason for this is that the clinical symptoms of radiation lesions of the digestive tract are very pronounced. According to foreign physicians, chiefly Japanese and American, who examined large numbers of people in Hiroshima and Nagasaki, the radiation sickness from which people suffered after explosion of the atom bombs was characterized, among other things, by leukopenia, anemia, leukemia, adynamia, dystrophy, and hemorrhagic tendencies; by nervous, cardiovascular, and sexual disorders; and by marked impairment of digestive functions (Warren, 1946; Dunhan, Cronkite, Leroy, and Warren, 1951; Tsuzuki, 1953; Kusano, 1954; Dambrin, 1955; Sears, 1955; Marhefka, 1955; A. V. Kozlova and E. I. Vorob'ev, 1956).

It has been observed that within a few hours of exposure most persons receiving doses of 300 to 1000 r develop nausea, vomiting, and diarrhea, which disappear in one or two days and then return at the height of radiation sickness. Other symptoms include marked anorexia and progressive loss of weight. A. N. Gamaleya and M. D. Donskoĭ (1954) mention the development of profuse diarrhea, necrotic ulcers of the buccal mucosa, stomatitis, and symptoms of paralytic intestinal obstruction.

Severe lesions of the digestive system were observed during the course of radiation sickness in persons exposed to radioactive fallout after the 1954 hydrogen bomb test on Bikini atoll (Arnold, 1954; Koyama and Kumatori, 1955; Mikamo, 1956; others). Digestive disorders included marked anorexia, nausea, vomiting, meteorism, disturbed secretory and motor activity of the gastrointestinal tract, stomach pain, acute weight loss, exhaustion, and several local and general inflammations in the alimentary canal.

A similar picture has been described by other investigators who observed persons after brief contact with intense ionizing radiation following the breakdown of an experimental reactor at Los Alamos research laboratory and after prolonged contact with such radiation (from being present during treatment with X-rays or radium or from working with isotopes).

According to L. Hempelmann, H. Lisco, and D. Hofman (1954), impairment of gastrointestinal activity in nine persons exposed during the course of an experimental chain reaction manifested itself variously, depending upon the radiation dose received. Seven men exposed to X-ray doses ranging from 31 to 390 r and to 0.18 to 26.6 r of gamma rays suffered only minor disorders. Another man, who received 480 r of X-rays and 110 r of gamma rays, complained of nausea and repeated vomiting the first day after the radiation. The next day he suffered prolonged periods of hiccuping. Two days later, his appetite, which had been absent, returned, but

he could not eat owing to inflammation of the buccal mucosa. He became flatulent on the 10th day and his abdomen was tender, especially in the right upper quadrant. From the 12th day until he died 24 days after exposure, he had liquid stools, severe stomatitis, and weight loss. The ninth patient died nine days after exposure to 1930 r. He developed nausea and vomiting soon after exposure and, by the end of the week, anorexia, jaundice, and collapse. At autopsy the intestine was found to be obstructed.

According to A. K. Gus'kova and G. D. Baĭsogolova (1955) who observed two patients with acute radiation sickness after total-body external gamma and neutron irradiation of 300 to 450 r, one man suffered nausea, vomiting, and loss of appetite within 20 seconds of exposure, while the other man showed the same symptoms within a few minutes. These symptoms abated after repeated gastric lavage but returned the next day.

M. N. Pobedinskiĭ (1954), Yu. G. Grigor'ev (1956), and N. A. Kurshakov, and I. S. Glazunov (1955) state that nausea, vomiting, thirst, abdominal pain, diarrhea, tenesmus, and anorexia are the most pronounced symptoms of radiation lesions of the digestive organs. Several of these symptoms were also noted by A. M. Yugenburg, L. G. Peretts, and R. S. Mostova (1933) in patients after external local irradiation.

According to N. N. Rynkova (1956), the impaired gastrointestinal activity observed during acute human radiation sickness is identical with the clinical picture of gastritis and enteritis. Changes in secretion and in enzyme activity of the intestinal juice parallel changes in the dynamics of nervous processes in the cerebral cortex, the extent of the changes varying with the stage of the disease.

We see, therefore, that ionizing radiation injury causes, among other things, serious impairment of activity in the digestive system, the effects remaining to some extent for many months and even years after clinical recovery. Disorders of gastrointestinal activity also occur in chronic radiation disease resulting from the prolonged action of radioactive substances taken into the organism, or from systematic exposure to small but greater than maximum permissible doses of external radiation from gamma rays, X-rays, or neutrons.

With a mild, chronic radiation sickness, the appetite diminishes and dyspeptic symptoms and meteorism appear. After an initial period of hyperfunction, gastric activity is marked by hyposecretion and achylia. In a moderately severe case, there are more marked metabolic disturbances: appetite reduction, regurgitation, pressure and heaviness in the gastric region, occasional diarrhea, decrease in the enzymatic activity of the digestive juices, heightened muscle tone of the large intestine, and stasis of chyme in the ileocecal region. In a severe case, the above symptoms are both more pronounced and more constant.

The chronic course of the disease, according to N. N. Rynkova (1956), is accompanied by decreased gastric and pancreatic secretion, weakened hepatic detoxifying ability, and impaired gastrointestinal motility. Z. A. Zedgenidze (1956) notes a "gastric paresis" during the first 24 hours, which disappears during the latent period of the disease, being followed by normal decreased motility. Paresis of the gastric and intestinal muscles, however, reappears at the height of the disease. Such undulation of the pathological processes has also been observed in the changes in gastric secretion. This reflects the wavelike or cyclic course of radiation sickness in general (N. A. Kraevskiĭ, 1955).

The disruption of digestive activity observed during radiation sickness of varying severity takes place against a background of impaired function of the central and peripheral nervous systems of hematopoiesis, of the cardiovascular system, the endocrine glands, kidneys, skin, and other organs, together with serious metabolic disturbances and dystrophy of cells and tissues. The course of the disease is subsequently complicated by the development of various infectious or septic processes which frequently are the direct cause of death. Autopsy of those dying of radiation sickness reveals the presence of profound injuries to the digestive organs (Bloom, 1947; Tullis and Warren, 1947; Liebow, Warren, and de Coursey, 1949; Brugge, 1952; T. Sears, 1955; N. A. Kraevskiĭ, 1955, 1957). Histological examination reveals evidence of changes in the mucosa of the gastrointestinal tract (the small intestine and ileum in particular), destruction of the glandular apparatus, and intramural nervous and vascular formations.

Vomiting, lowered food excitability, inflammation and ulceration of the gastrointestinal mucosa, and other signs of radiation injury to the digestive system have also been observed in animals exposed to ionizing radiation (P. D. Gorizontov, 1955; Yu. N. Uspenskiĭ, 1957; S. R. Perepelkin, 1957; and others). For example, in a monkey exposed to a single total-body dose of 400 to 800 r, disruption of digestive activity is the clearest sign of radiation sickness.

Severe radiation lesions of the gastrointestinal tract also occur after local irradiation of the abdominal region (Régaud, Nogier, and Lacassagne, 1912; Warren and Whipple, 1922; Graham, 1939; Bond, Swift, Allen, and Fischler, 1950; Quastler, Lanzl, Keller, and Osborn, 1951; Yu. N. Uspenskiĭ, 1957).

In concluding this brief survey, we should like to stress the fact that radiation lesions of the viscera, including the digestive organs, are associated with pronounced symptoms of nervous disorders, especially in the higher divisions of the central nervous system.

In 1957, 354 patients with radiation lesions were observed by M. P. Domshlak, Yu. G. Grigor'ev, N. G. Darenskaya, L. B. Koznova, and G. F. Nevskaya. Besides changes in blood composition,

cardiovascular function, and in the activity of the digestive system (anorexia, regurgitation, thirst, decreased taste acuity, urge to vomit, salivation, diarrhea, abdominal pain), they also found changes in the patient's general condition and nervous disorders (rapid fatigability, heightened irritability, sleepiness or insomnia, apathy, headaches, vertigo, olfactory disturbances, hidrosis, pruritus, chills, etc.).

A. L. Morozov, E. A. Drogichina, M. A. Kazakevich, N. I. Ivanov, and S. F. Belova (1957) examined flaw-detecting personnel, radiographers, nurses, and laboratory technicians exposed to ionizing radiation in industrial X-ray laboratories and noted a variety of symptoms of functional nervous disorders: neurasthenia, adynamia, easy fatigability, decreased vibration sensitivity, elevated threshold of olfactory excitability, impaired mobility and imbalance of nervous processes in the cerebral cortex, a weakening of internal inhibition, the appearance of hypnotic states, a dominance of parasympathetic over sympathetic reactions, and changes in the nature and tone of vascular reflexes.

A. V. Kozlova, V. M. Malenkova, E. V. Karibskaya, and T. S. Seletskaya (1957) examined 140 persons after prolonged exposure to ionizing radiation and noted that the patients with various symptoms of chronic radiation sickness, including gastrointestinal disturbances, were also suffering from a variety of nervous disorders that became manifest before pain arose in the viscera.

A thorough examination of persons chronically irradiated with small doses of ionizing rays (occasionally five to ten times above maximum permissible levels—over 0.05 r or 50 mr a day) showed signs of central nervous system functional disorders (V.I. Kuznetsov, V. A. Baranov, V. V. Fialkovskiĭ, K. K. Smirnov, G. I. Dovzhenko, G. S. Goryushin, N. I. Shcherbakov, E. G. Zhuk, N. V. Butomo, P. V. Preobrazhenskiĭ, and K. B. Tikhonov, 1957). These disorders were manifested in asthenia, polyneuritis, weakening of active cortical inhibition, lowered efficiency of cortical cells, and organic changes in the central nervous systems. They were usually associated with decreased salivation, hemorrhage and ulceration of the buccal mucosa, changes in the otorhinolaryngological organs (pharyngitis, neuritis of the auditory nerve, paralysis of the laryngeal muscles, epistaxis), eyes (photophobia, burning and dryness, tiny hemorrhages in the palpebral and ocular conjunctiva), and viscera (neurocirculatory hypotonia with signs of bradycardia, increase in the rate and minute volume of the heart, gastric hyposecretion, dyskinesia of the small and large intestines, mucosal hemorrhage of the small intestine, leukopenia with neutropenia or lymphopenia, brittleness of vascular walls, amenorrhea or menorrhagia in women, mucosal hemorrhage of the urinary bladder, etc.).

I. S. Glazunov and A. M. Vyalov (1956) observed impairment of thermoregulation in persons suffering from radiation injury.

All of the above clinical observations on radiation lesions of the viscera and the higher divisions of the central nervous system are highly significant in that they suggest an approach to the experimental investigation of many radiophysiological problems. It is quite evident that a study of radiation injury to the digestive system with a simultaneous analysis of changes in digestive and nervous functions is the most satisfactory kind of physiological experimentation and the most valuable to clinical practice.

Moreover, digestive disorders, which constitute a major factor in radiation sickness, greatly complicate and aggravate the general course of the pathological processes and at the same time weaken the resistance of the organism in its struggle against complications of radiation sickness. Thus, the physician has the important practical task of returning the digestive organs to their normal state at the same time that he is applying general therapeutic measures. This can be done quickly and effectively only if he is sufficiently familiar both with the physiology of digestion and with radiation lesions of the alimentary canal.

PART I

Functional Characteristics of the Digestive Organs after Exposure to Ionizing Radiation