THE RELATIONSHIP BETWEEN THE LOCALIZATION OF RADIATION INJURY AND THE FUNCTIONAL STATE OF AN ORGAN

COMMUNICATION 2

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In a previous investigation [9] we showed that the degree of manifestation of a radiation injury of the kidneys and its localization are determined by the magnitude and character of the functional load on the nephrons at the moment of irradiation. An increase in the renal function during the period of exposure to ionizing radiation causes the radiation lesion to be localized mainly in the parenchyma of the kidney. The strict regularity of this relationship is firm evidence that the state of increased function intensifies the degree of manifestation of radiation injury to an organ. These observations enabled us to employ the same experimental model, with slight variation of the experimental conditions, in order to attempt to solve certain problems of the pathogenesis of radiation sickness. We wished to find out whether the character of the course of radiation sickness is determined during the actual period of exposure to the radiation or whether the "after-action" period is of decisive importance. It was a working hypothesis in the investigation that, if a functional loading of the kidneys, applied in the period of development of radiation sickness, produces a more severe radiation injury of the nephrons, this is proof of the greater importance of the period of establishment of radiation sickness. In the event of the converse results of the investigations – absence of increased severity of injury to the renal parenchyma – it could be considered that the degree of structural change of the organ and the character of the course of the disease are determined purely by the direct action of ionizing radiation on the animal body.

METHOD

The investigations were conducted on sexually mature C57 pure line mice, weighing 22-28 g. About 350 animals of both sexes were under observation. For single whole-body irradiation of the mice we used an RUM-3 apparatus under the following conditions: voltage 180 kv, current 10 ma, filter 0.5 mm Cu + 1 mm Al, dose rate 45-48 r/min, focus distance 30 cm, dose 1400 r (measured in the air with a GRI dosimeter). During irradiation each mouse was placed in a separate cardboard box, measuring 7 x 5 x 4 cm. The experimental and control animals were irradiated simultaneously. On the first, second and third days after irradiation the experimental animals received intraperitoneal injections of euphyllin. The size of each dose of euphyllin (1.2 mg of the standard preparation in ampules, in 1 ml water) was determined experimentally; it produced increased diuresis without causing morphological changes in the renal parenchyma. We measured accurately the survival period of the experimental and control animals after irradiation; we made macro- and microscopic studies of the material, using various histological methods for this purpose.

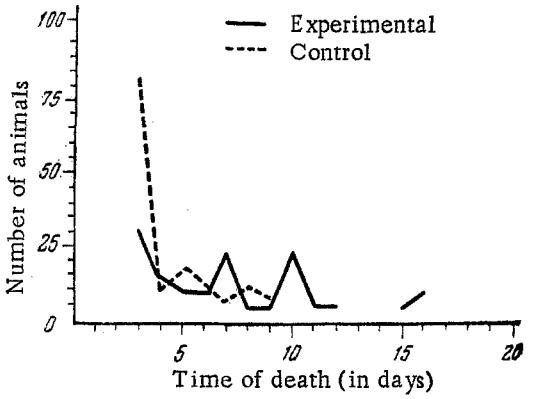

Fig. 1. Duration of life of experimental and control animals.

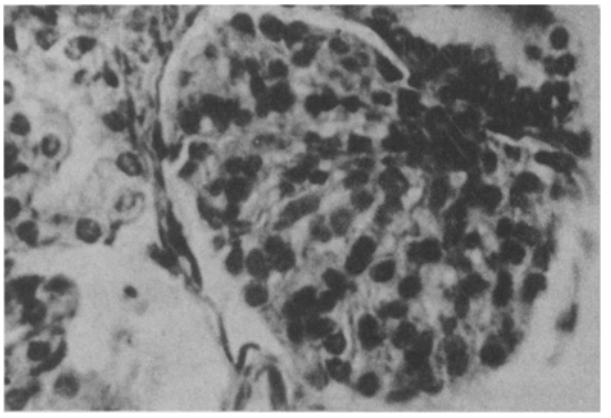

Fig. 3. Enlargement of the glomerulus and increase in number of its nuclei. Photomicrograph. Ocular 12×, objective 45×. Stained with eosin-hematoxylin.

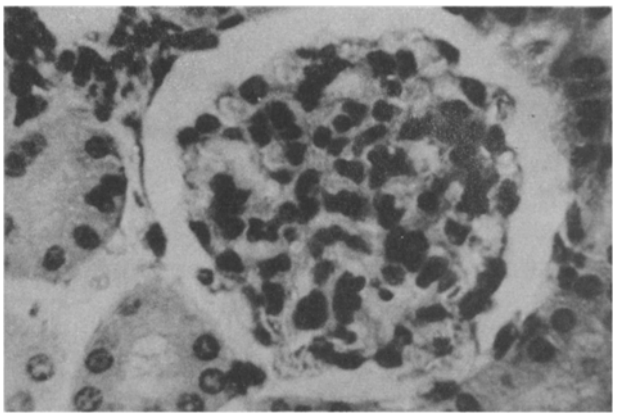

Fig. 2. The congested glomeruli retain the structure of the vascular network. Photomicrograph. Ocular 12×, objective 45×. Stained with eosin-hematoxylin.

RESULTS

All the experimental and control animals died from radiation sickness, but there were certain differences in the duration of its course and in the severity of the morphological changes in the kidneys. The survival period of the control animals varied from 3 to 9 days; their mean duration of life was 4.35± 0.43 days. Considerable uniformity of the experimental material was found; in the great majority of cases the mice died on the third day. This can be seen clearly in the diagram, which is characterized by a single sharp fall on the curve (Fig. 1). Death of the experimental animals took place between the third and 16th days, although in one case, which we excluded from the statistical treatment of the results, death was observed even 30 days after irradiation. The mean duration of survival of the experimental animals was 6.8± 0.66 days. This group of cases showed considerable variation in the survival period of the mice, giving a drawn-out curve with many peaks (see Fig. 1). It must be emphasized that in almost every case the duration of survival of the animals receiving euphyllin was longer than that of the control animals. The only exception was one case in which the control mouse lived longer than the experimental mouse and no radiation injury was present in the kidneys.

The macrosopic material was characterized by great constancy of the morphological changes, which were typical of acute radiation sickness. Emaciation was always marked, more so when the survival period of the animals was prolonged, and was accompanied by a hemorrhagic diathesis and atrophy of the hemopoietic tissue. If the mice died early the predominant changes were those typical of radiation injury in the intestine.

In the experiment on mice receiving the diuretic after irradiation, in the great majority of cases (98%) the typical morphological changes of radiation injury were absent from the renal parenchyma. When the animals died at an early period (between 3 and 5 days) the glomeruli were distinguished by severe congestion; their vascular network retained its clear pattern, and the endothelium was well defined (Fig. 2). The structure of the tubules remained unchanged. With a longer period of survival of the mice after irradiation (over 6 days) large tubules with a high proportion of nuclei were often seen (Fig. 3). The mean diameter of the tubules in the experimental animals was 53± 1.7μ and in the controls 49± 1.6 μ. Many nuclei of the enlarged tubules showed hyperchromatosis and were of a considerable size. The epithelial portions of the nephrons retained their usual structure. In three cases radiation injury of the kidneys was also observed in the group of experimental animals; its morphological picture was restricted, however, to a slight swelling and basophilia of the walls of the vascular network of the glomeruli and to signs of necrobiosis in the individual nuclei. Identical changes could also be seen

in certain arterioles of the interstitial tissue of the kidneys. Foci of necrobiosis were present in the epithelium of the main divisions of the tubules.

In all but one of the control animals (0.7%) the typical picture of radiation injury was seen. The walls of the arterioles of the renal glomeruli and interstitial tissue were very swollen, homogeneous and basophilic. In many vessels the endothelium was in a state of necrobiosis. In the epithelium of the tubules there were marked dystrophic changes, turning into necrosis. In some cases the lumen of the tubules contained numerous cylinders. Small hemorrhages were often present.

In order not to overload the articles with factual matter, we shall state only that identical results were obtained in experiments in which caffeine was used as the diuretic. The administration of mercusal (a mercurial diuretic) to irradiated animals led to an obvious shortening of their period of survival and greatly increased the morphological signs of radiation injury to the kidneys. The observations are in full agreement with the pharmacological data that mercusal may only be used in the absence of kidney disease [1], otherwise the toxic diuretic will only aggravate the pathological changes in the organ.

The results of our experiments were thus somewhat unexpected, and in some ways did not correspond to the original idea of the investigation. The increased functional load on the kidneys after irradiation brought about a statistically significant ($t = 3.175$) lengthening of the period of survival of the irradiated animals and almost abolished the morphological changes in the renal parenchyma. The prolongation of the course of the radiation sickness was accompanied by a change in its morphology. The bulk of the control animals showed the "intestinal" form of radiation sickness, which, according to the literature [7, 9, 10, 11], is characteristic of the action of massive doses of ionizing radiation. In the experimental animals other forms of manifestation of radiation sickness predominated, the main localization of the typical morphological changes being in other organ systems, primarily in the hemopoietic tissue. In other words, in these cases the character of the morphological signs of the disease corresponded to the usual pattern of injury resulting from exposure to much smaller doses of irradiation. In these experimental conditions, therefore, the administration of diuretics caused some decrease in the severity of the manifestations of radiation sickness.

Comparison between these facts and the results of previous investigations shows, in our opinion, that the direct, injurious action of ionizing radiation is of great importance in the pathogenesis of radiation sickness. At the same time, however, it is impossible to ignore the role of the "after-action", an important element of which is evidently the toxic products of tissue destruction. The excretion of these "toxic factors" [4, 5, 6, 8] by the kidneys, functioning at a higher level of intensity, was also probably responsible for the sufficiently demonstrative results of these various investigations.

Our observations differ from the results of work carried out in S. S. Vail's laboratory [2, 3]. In these investigations an increase in the severity of the radiation pathology was observed when the function of the heart and gastro-intestinal tract was loaded after irradiation of the animals. The obtaining of contrary results from similar experiments evidently depends on essential differences in the character of the function of the organ system studied. The favorable influence of increased work of the excretory organ on the course of radiation sickness illustrates well the role of toxic substances in the pathogenesis of the disease. It can be concluded from this observation that the course of radiation sickness may be actively influenced, in the sense of decreasing the severity of its manifestations, by the repeated administration of diuretics acting upon the vascular elements of the nephrons.

SUMMARY

An attempt was made to study the effect of increased diuresis, induced following irradiation, upon the morphology of the kidneys. Euphyllin was repeatedly administered to mice of the C57 lineage following general irradiation (apparatus RUM-3, voltage – 180 kv, current – 10 ma, filter – 0.5 mm Cu + 1 mm Al, intensity – 45-48 r/m, dose – 1,400 r). Euphyllin administration considerably prolonged the animals' life span and protected the kidneys from radiation injury. The effect of a diuretic is regarded by the authors as being due to the excretion of the toxic products of tissue disintegration (appearing as a result of the action of ionizing radiation).

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*Original Russian pagination. See C. B. translation.