

THE STATE OF THE RECEPTORS OF THE HINDLIMB IN DOGS DURING THE DEVELOPMENT OF A COLLATERAL CIRCULATION AND OF RADIATION SICKNESS

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Every operation is accompanied by division and ligation of blood vessels, which results in a change in the direction of the blood flow in certain areas of the body.

The course of development of collaterals in various organs and parts of the body has been established by experimental research and also by clinical observation.

The problem of the surgical treatment of injuries of various organs in irradiated subjects is indissolubly connected with the development of a collateral circulation.

Our investigations [4, 5], at first carried out in rats and subsequently in dogs, showed that the development of collaterals in the skin, muscles and nerves of irradiated animals takes place no less satisfactorily than in control animals observed after the same intervals of time. It was concluded that the plasticity of the blood vessels in animals suffering from radiation sickness evidently remains at a level capable of ensuring the development of a collateral circulation. Similar findings were obtained [1] during operations on the main blood vessels (circular suture, venous autografting) in dogs suffering from radiation sickness.

It is clear that the action of ionizing radiation is a factor mobilizing the potential resources of the blood vessels of the body. Under these circumstances new conditions are, of course, created for the structural and functional adaptation of collaterals.

The development of a collateral circulation in irradiated animals is thus an anatomo-physiological problem and requires complex investigations for its solution. Until recently the development of collaterals in irradiated animals has not been studied in connection with any definite function of the corresponding organ. Meanwhile it has been established in physiological experiments by D. M. Gzgzyan [2] that the afferent impulses from the limb in irradiated dogs change in accordance with the time elapsing after irradiation, i.e. with the period of development of radiation sickness.

We investigated the functional state of the receptor apparatus of the hindlimb in irradiated dogs during the development of a collateral circulation. In this way we attempted to examine the possible mechanism of action of ionizing radiation on the development of collaterals.

METHODS

Experiments were carried out on 32 dogs. In the course of one day the animals were subjected to whole-

body irradiation in a dose of 450 r (conditions: 185 kv, 15 ma, 0.5 mm Cu) and to the operation of resection of the femoral artery in one (the right or left) limb; the other limb usually served for comparison and control purposes.

Research by I. D. Lev [3] showed that, after resection of the femoral artery in dogs, collaterals develop mainly in the posterior group of thigh muscles, receiving blood from the hypogastric artery through branches of the caudal gluteal artery (Fig. 1). The anatomical basis of this fact is that the hindlimb of the dog, in contrast for example to the lower limb in man, is supplied with blood from two systems of arteries: the femoral and caudal gluteal arteries.

We therefore studied the afferent impulsionation from the receptors of both hindlimbs after various intervals of time by the method of perfusion through the caudal gluteal arter, for the femoral artery in one of the limbs was removed during operation. Under chloralose or urethane anesthesia, both hindlimbs of a dog were separated from the trunk. The muscles were divided near their origins, together with the femoral and obturator nerves, and careful hemostasis was observed. The femoral artery of the unoperated limb was ligated and divided between two ligatures before the beginning of perfusion. The femur was disarticulated at the hip joint. The limbs were left connected to the trunk only by the sciatic nerve.

Both limbs were perfused through cannulas inserted into the caudal gluteal artery with Tyrode solution, enriched with oxygen and warmed to 38-39°. The perfusate flowed out through the femoral veins. Both limbs were thus kept under identical experimental conditions, so that a comparative study could be made of the afferent impulsionation from their receptors. We may mention that in one limb (in which the femoral artery had been divided) the development of a collateral circulation had already reached a certain level, whereas the blood vessels of the other limb had not undergone any preliminary changes. We thus expected to find differences in the reflexes from the receptors in the two limbs under examination.

The presence of an afferent impulsionation was judged by reflex changes in the arterial pressure and respiration arising after the injection of chemical stimulants into the blood stream of the limbs. As stimuli of the chemoreceptors we used a 2% solution of KCl and a 1 : 1000 solution of nicotine. These substances were injected into the per-

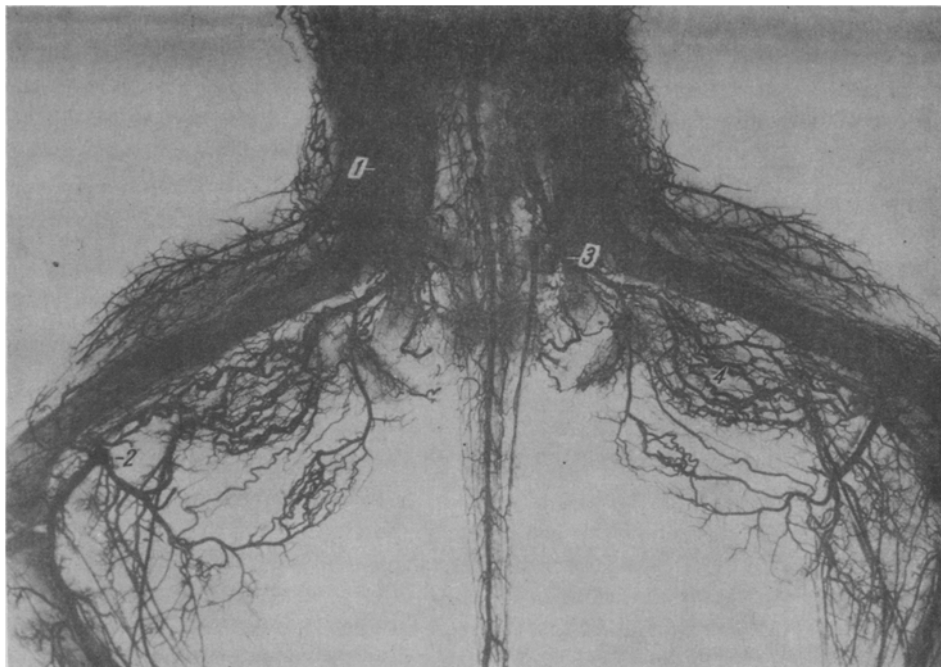


Fig. 1. Development of collaterals in the hindlimbs of a dog after resection of the femoral arteries (roentgenogram). 1, 2) Proximal and distal cut ends of the femoral artery; 3) caudal gluteal artery; 4) collaterals developing from the anastomoses of the caudal gluteal system of arteries with the popliteal artery.

fusate, directly into the cannula inserted into the caudal gluteal artery.

The arterial pressure was recorded with a mercury manometer in the left carotid artery. Respiration was recorded by means of a Marey's capsule, communicating with a corrugated tube bound around the animal's thorax. These indices, together with the zero line, the marker of injection of the drugs and the time marker were recorded on the kymograph.

RESULTS

After whole-body irradiation with a dose of 450 r, the dogs began to develop acute radiation sickness. The animals' condition gradually deteriorated, and by the 11th-12th day after irradiation, they could not usually withstand the acute experimental conditions, which had to be limited to these times. In all three series of experiments were carried out: at intervals of 4-6 days, 8-9 days and 11-12 days after irradiation. The blood was examined in all the dogs before the experiment (white cell count, ESR, hemoglobin).

On the 4th-6th day after operation and whole-body irradiation of the dogs, the changes observed in the afferent impulsion from the limbs, operated and unoperated, were not always in the same direction. In some animals there was a greater increase in the reaction from the receptors of the limb in which collaterals were developing. In these cases the receptors of the operated limb reacted to all the doses of the stimulus that were used, whereas the receptors of the other (control) limb did not respond

to ordinary (2 ml of a 2% solution of KCl) doses; a perceptible afferent impulsion was elicited only by the use of double doses of the stimulus. In other animals of the same series of experiments, on the other hand, the afferent impulsion from the control limb was more pronounced than that from the operated limb. It must be assumed that, during this (latent) period of radiation sickness, changes were observed in the afferent impulsion to the central nervous system, which interfered with the regulatory activity of the latter.

At this time the collaterals of the caudal gluteal arterial system in the operated limb could still not be detected by anatomical methods, and hardly differed from the usual anastomoses of the arteries of this system in normal animals (i.e., in the control limb).

In the next series of experiments, 8-9 days after whole-body irradiation of the dogs, it was clearly seen that the receptors of the operated limb reacted more strongly to the injection of the stimuli into the perfusion fluid than did the receptors of the control limb (Fig. 2, a). This was particularly demonstrable after the injection of small doses of the stimulus (1 ml of a 2% solution of KCl), which evoked more pronounced reflexes from the operated limb than from the control (Fig. 2, b).

It was apparent that the reception from the operated limb, in which collaterals were continuing to develop, was more increased than that from the opposite limb, in which collaterals were continuing to develop, was more increased than that from the opposite limb, in which the system of anastomoses of the caudal gluteal artery began

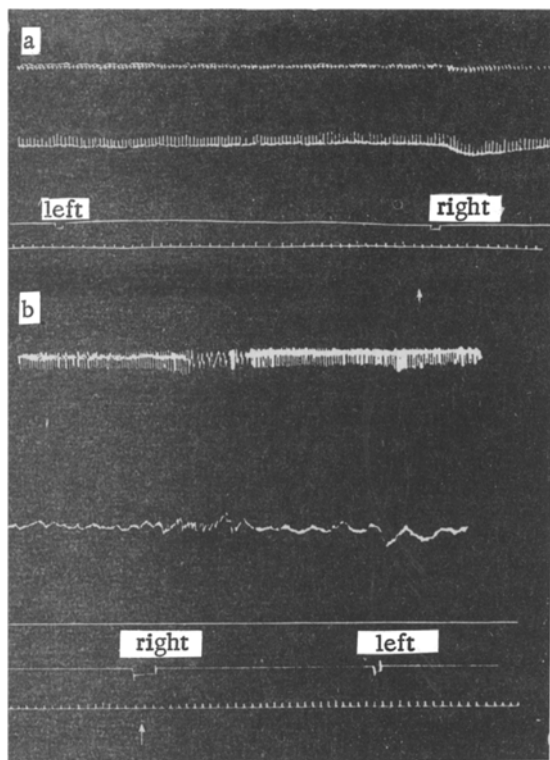


Fig. 2. Changes in the arterial pressure and respiration on the 8th-9th day after resection of the femoral artery () and whole-body irradiation in dogs. Significance of the curves (from above down): Recording of respiratory movements; recording of arterial pressure; marker of injection of stimulus and zero line of arterial pressure; time marker (5 sec). a) After injection of 2 ml of 2% KCl; b) after injection of 1 ml of 2% KCl.

to function intensively only during the time of the acute experiment.

The results of this series of experiments confirmed the fact, obtained by anatomical methods of investigation [4, 5], that the plasticity of the blood vessels, without which the development of collateral channels of circulation cannot be contemplated, is evidently maintained at an adequately high level even during the conditions of acute radiation sickness. The blood analyses showed that the white cell count in the peripheral blood of these animals fell to 3000-850/mm³ (in one experiment 750), and the ESR reached 18-43 mm in 1 hour.

In the third series of experiments the dogs were included which survived 11-12 days after whole-body irradiation, when the period of crisis of radiation sickness was beginning. The white cell count fell to 600-350/mm³. The experiments on two dogs were performed at an arterial pressure of 70 and 35-40 mm Hg. The animals' condition had deteriorated to such an extent that some of them could not withstand the acute experimental conditions, but died soon after separation of the hindlimbs from the trunk, with a sharp fall in the arterial pressure.

In none of these experiments was it possible to obtain appreciable changes in the level of the arterial pressure and in the respiratory movements after the injection of any dose of the stimulus whatever (up to 20 ml of a 2% of KCl solution) into the artery on either the operated or the control limbs. At this time, meanwhile, as anatomical investigations showed (see Fig. 1), the development of collaterals continued. It must be assumed that the severity of the radiation sickness had a profoundly destructive effect on the function of the receptors, from which the afferent impulsation was sharply reduced under these conditions.

The results of the three series of experiments which have been described suggest that, during the development of a collateral circulation in irradiated dogs, changes take place in the afferent impulsation from the receptors of the limbs, as shown by: the lability of the reflexes, which is observed during the first 4-6 days of development of the collaterals and the radiation sickness; the increase in the reflexes, which corresponds to the further development of the collateral channels; and the depression of the reflexes commencing on the 11th-12th day of the acute radiation sickness while the process of collateral development continues.

A common tendency of the first two phases is the increase in the strength of afferent impulsation as the collaterals develop in the limb.

At the height of the disease a lack of correlation developed between the degree of formation of collaterals in the limb and the functional state of its receptor apparatus. What was the possible reason for this phenomenon? Where did the inhibition of the impulses take place: at the periphery, in the limb itself or in the central nervous system?

We felt that an attempt could be made to answer these questions by carrying out special experiments on dogs in which the resection of the femoral artery was performed simultaneously on both hindlimbs, and only one limb was exposed to x-ray irradiation in a dose of 450 r. The other limb thus acted as a control for comparison.

Eleven days after operation and local irradiation, changes could be observed in the reactions to the injection of ordinary doses of the chemical stimulus only from the unirradiated limb. Only when the dose of KCl was 5 ml were changes seen in the arterial pressure level and the respiratory movements from the irradiated limb.

The results of these experiments may be interpreted as showing the direct influence of ionizing radiation on the receptor apparatus of the limb. A further check had to be made of the hypothesis that depression of the central ends of the analyzers arises in the dogs on the 11th-12th day after whole-body irradiation.

For this purpose, in dogs exposed to whole-body irradiation and to unilateral operation on the limbs (as in the principal series of experiments), the sciatic nerve was stimulated after 11-12 days by means of an induction current (voltage 6 v, distance between coils 20 cm),

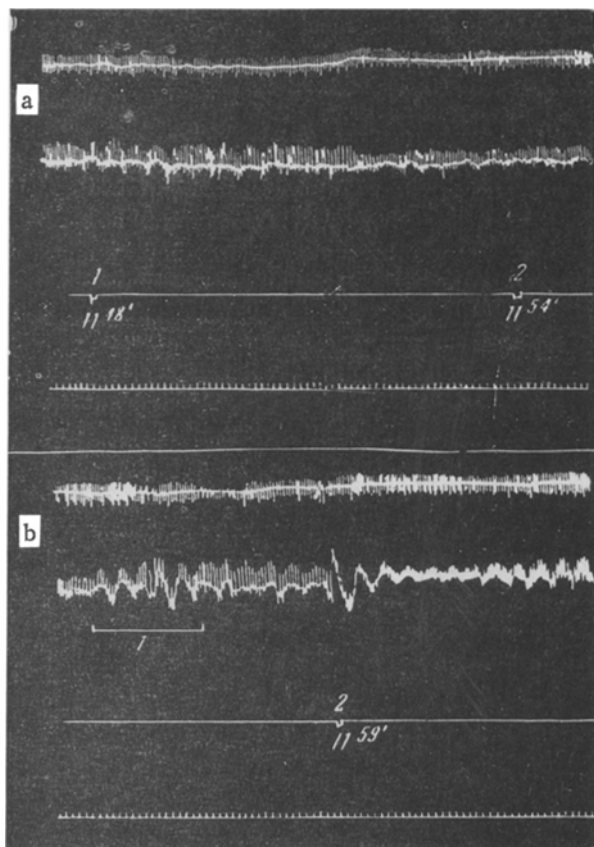


Fig. 3. Changes in the arterial pressure on the 11th day after resection of the femoral arteries and local irradiation of one hindlimb. a) Recording of respiration and arterial pressure after injection of 2% KCl: 1) 2 ml; 2) 3 ml; b) the same after insertion of electrodes and stimulation of the sciatic nerve with an electric current (2).

for no changes in the reflex reactions to chemical stimulation from the receptors of the limb could be obtained (Fig. 3,a). By the mere placing of the electrodes under the nerve, not to mention the time of actual passage of the current, a sharp increase took place in the amplitude of the cardiac contractions, with a fall in the arterial pressure and a slowing of respiration (Fig. 3, b). These experiments showed that whole-body irradiation of an animal is accompanied both by disturbances of the function of the central nervous system and by direct change in the reflex apparatus of the organs and tissues of the limb.

Our experiments provide new proof of the fact that the function of an organ depends not only on the number and diameter of the arteries supplying it, but also on the state of its nervous apparatus. Whereas an anatomical study of the development of collaterals during radiation

sickness shows that their structural adaptation remains at a high enough level for the formation of a collateral circulation, their functional adaptation does not always proceed along the same lines, but changes in accordance with the severity (or stage) of the radiation sickness. So far as the causes of these changes are concerned, besides the local influence of ionizing radiation on the receptor apparatus, demonstrated in our experiments, it cannot be denied that central inhibition of impulses also arises under these conditions. The combination of both phenomena creates the complex picture of the mechanism of the reflex activity of the animal in acute radiation sickness.

SUMMARY

The authors studied the effect of irradiation (450 r) on the condition of the receptors of the posterior limb of the dog in which a collateral circulation developed after resection of the femoral artery. The change of the afferent impulsation in the operated limb was shown by: a) The lability of the reflexes observed during the first 4-6 days of development of collaterals in radiation sickness; b) the increase of the reflexes corresponding to the further development of the collateral circulation, and, c) depression of the reflexes beginning with the 11th-12th day from the onset of acute radiation sickness with the continuation of the process of development of collaterals.

The authors came to the conclusion that the structural adaptation of collaterals was adequate for the development of collateral circulation but its functional adaptation did not follow a parallel course and changed in accordance with the stage of radiation sickness.

LITERATURE CITED

- [1] P. I. Atavin, Operations on Major Blood Vessels in Acute Radiation Sickness. Author's abstract of candidate dissertation [in Russian] (Leningrad, 1957).
- [2] D. M. Gzgzryan, Abstracts of Proceedings of an All-Union Scientific Conference on Combined Radiation Injuries ([in Russian] (Moscow, 1958) p. 25.
- [3] I. D. Lev, Anatomy of the Collaterals of the Pelvic Extremity of the Dog and the Effect of Removal of the Afferent Nerve Supply on their Development. Author's abstract of candidate dissertation [in Russian] (Leningrad, 1949).
- [4] I. D. Lev, Abstracts of Proceedings of a Scientific Conference [in Russian] (Leningrad, 1957) p. 44.
- [5] I. D. Lev, Abstracts of Proceedings of the Sixth All-Union Congress of Anatomists, Histologists and Embryologists [in Russian] (Khar'kov, 1958) p. 384.