EFFECTS OF INTRAVENOUS INJECTIONS OF RADIUM BROMIDE.

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Plate XVI.

The present study was undertaken with a view of determining in a general way the effects of intravenous administration of radium upon the circulation and respiration. The problem was suggested to us by Dr. William J. Gies, under whose guidance a number of researches, dealing with the more extensive question of the action of radium upon animal and vegetable cells, have recently been carried on in the laboratories of Columbia University.[1]

For the radium used in these experiments we are greatly indebted to Mr. Hugo Lieber. It was supplied to us in the form of the bromide, in preparations of 240, 1000, and 10,000 activities. The strength of the solution used was the same in all cases. It contained 45 mg. of the dry substance in 25 c. c. of the solvent; each cubic centimeter of the solution, therefore, contained 1.8 mg. of the radium preparation.

The amount of the radium present varies directly with the radio-activity. Preparations of 1,500,000 activity are said to represent pure radium bromide.[2] Taking this figure as the standard of purity, 1.8 mg. of the radium preparation of 10,000 activity contained approximately only 0.0126 mg., the same quantity of the preparation of 1000 activity contained 0.00126 mg. and a like amount of the preparation of 240 activity only 0.00036 mg.

[1] Preliminary communications of the results were made last May. See Gies and collaborators: *Proceeding of the Society for Experimental Biology and Medicine*, 1905, ii, 86; also, *Science*, 1905, xxi, 986; *American Medicine*, 1905, ix. 1026; *Medical News*, 1905, lxxxvii, 520.

[2] Rutherford, *Radio-activity* (Second Edition), 1905, p. 14, "No definite results have yet been given on the activity of pure radium, but the Curies estimate that it is about one million times that of uranium and may possiby be higher."

of actual radium bromide. Expressed in terms of the element radium (atomic weight = 225), each cubic centimeter of the solutions of the different preparations used in these experiments represents respectively about 0.00739, 0.00074, and 0.000178 mg. of radium. It must also be mentioned beforehand that the effect of these radium preparations may be due not alone to the radium, but to its disintegration products, namely, emanation,—radium A, radium B, radium C — or to the radiations given off by these. As will be brought out later, there appears to be a distinct difference between the action of the perfectly fresh solution and one that has been left standing for some time in an open receptacle. Whether this difference is due to an increased or decreased amount of emanation in the solution has not been determined as yet.

The substance was dissolved in distilled water, perfectly fresh solutions, heated to body temperature, being employed for the injections. The experiments were performed upon dogs weighing from three to seven kilos. Light ether narcosis was employed. The blood pressure was recorded by a mercury manometer connected with the carotid artery and the respiratory movements by means of a modified pneumographic arrangement. The injections were made into the facial vein.

A number of preliminary tests were made to determine the influence of the intravenous injections of such quantities of distilled water as were made use of subsequently in the experiments with radium bromide. Only in those cases in which the injection was made with more than a moderate degree of rapidity could any effect upon the circulation be detected.

The radium bromide of 240 activity was employed in six experiments, approximately 10 c. c. of the solution, or 18 mg. of the preparation being administered in each case. Curve I, (Plate XVI) which forms only a small part of the entire record of Experiment I, may serve to show the character of the changes observed. It was obtained from a dog weighing four kilos and differs in no particular from the other records of this series. The injection began at A and was discontinued at B. Besides

the blood pressure (Pr) the curve also includes a record of the respiratory movements (R) and a time-tracing (Sec).

The blood pressure began to rise in all cases shortly after the beginning of the injection and continued to increase gradually until about 5 c. c. of the solution had been injected, or during a period of from thirty to thirty-five seconds. The length of the period intervening between the beginning of the injection and the appearance of the rise depended somewhat upon the rapidity with which the solution was injected. On the whole, however, it was rather brief, averaging about four or five seconds. The rise itself appeared as a rule rather abruptly and attained its maximum value in the course of about thirty-five seconds. The maximum increase here recorded amounted to 60 mm. Hg and the minimum rise to 20 mm. Hg, the average noted in the six experiments being 35 mm. Hg.

By comparing the normal frequency of the heart with its rate during the period of increased blood pressure, only very insignificant differences were brought out. If anything, a hardly recognizable inhibition had taken place, which, however, was more than compensated for by an increase in the force of the cardiac contractions. A study of the curves proves beyond question that radium bromide of this activity exerts a moderate tonic action upon the heart muscle. However, the greater force of the contractions is not at all sufficient to explain the marked increase in blood pressure. For this change, no doubt, a direct vaso-constrictor influence of the radium bromide upon the musculature of the blood-vessels must be held responsible.

The gradual rise in blood pressure, caused, as has just been stated, by a general constriction of the blood-vessels, was invariably interrupted after about thirty-five seconds by a very pronounced irregularity and inhibition of the heart. Relatively long diastolic periods were now followed in rapid succession by periods during which a number of short forcible contractions caused the mercury to rise far beyond any ordinary level, but in spite of the fact that the blood pressure attained at times quite extraordinary heights, its average value remained as a rule well below the height to which it had risen during

the period of vaso-constriction. As the experiment progressed, the pressure gradually became lower and lower and sank to zero shortly after the onset of the respiratory paralysis. It happened at times that the heart regained for a period of indefinite length a certain regularity of contraction, but even during these moments of partial restoration its frequency was very much less than normal.

A change in the rate of respiration during the period of vaso-constriction could not be detected. Shortly after the onset of the cardiac symptoms, however, the respiratory movements became distinctly less frequent and deep. As the experiment progressed, this inhibitory influence came more and more into prominence, until finally a complete respiratory paralysis resulted. The heart ceased beating shortly after the respiratory movements came to a standstill. When the lungs were inflated artificially soon after the onset of the respiratory paralysis, the heart action continued; respiration, on the other hand, did not become automatic again during the time of these experiments, i. e., within about ten minutes after the cessation of the natural respiratory movements.

Two experiments were made in addition upon dogs whose vagi had been divided beforehand. A difference in the effect of the radium bromide, directly ascribable to this operative measure, could not be detected, excepting, of course, a lesser prominence of the initial vaso-constrictor reaction. The latter change was due entirely to the pre-existing high arterial tension and blood pressure. Vagus stimulation remained effective throughout the experiment. These facts, therefore, tend to prove that the radium bromide does not exert a central, but rather a direct influence upon the substance of the heart.

Several tests were also made with radium bromide solutions that had been left standing in an open flask for about one week preceding the day of the experiment. It was found in all cases that these solutions had lost a good deal of their effectiveness.

The details of the experiments with radium bromide of 240 activity are given in the following table in conjunction with those

in which the preparations of 1000 and 10,000 activities were employed. Besides the weight of the animal and the amount of radium administered in each case, the table also gives comparative figures regarding the cardiac and respiratory frequency and the blood pressure during the different periods of the experiment.

THE EFFECT OF INTRAVENOUS INJECTION OF RADIUM BROMIDE SOLUTIONS.

	Exp.	Weight of dog K.	$RaBr_2$ injected. per mg.K	Normal			Period of constriction			Period of irregular heart action		
				Resp. rate	Pulse	Blood pr.	Resp. rate	Pulse	Blood pr.	Reps. rate	Pulse	Blood pr.
$RaBr_2$ 240 act.	1	3.4	5.3	9	90	88.6	8½	90	108.9	cessation	very irreg; cess.	
	2	5.0	3.6	12	85	77.5	12	85	121.0	"	"	"
	3	3.7	4.9	9	74	122.5	10	75	182.8	"	"	"
	4	4.3	4.2	11	78	103.7	11	76	146.0	"	"	"
	5	5.7	3.2	8	95	126.2	8	89	152.1	"	"	"
	6	4.6	3.9	12	82	114.9	12	82	139.3	very slow	"	"
$BaBr_2$ 1000 act.	7	4.0	2.5	14	80	136.8	13	78	169.0	cessation	"	"
	8	5.5	3.9	12	76	132.7	12	76	152.2	"	"	"
$RaBr_2$ 10,000act.	9	5.5	3.3	16	82	140.1	17	82	175.7	9	36	87.6
	10	5.2	3.6	17	86	114.8	17	82	126.5	10	47	102.2
	11	7.0	3.6	13	91	97.7	14	91	132.1	8	31	88.7
	12	5.5	3.4	18	80	122.1	17	80	135.6	8	41	75.2

As barium bromide forms so large a part of the radium bromide preparations, it was thought possible that the effects noticed in the preceding experiments might be due at least in part to this constituent. To test this assumption several experiments with pure barium bromide solutions were performed, the method being the same as the one described in an earlier paragraph of this paper.

Our results relative to the barium are entirely in harmony with those described by Mickwitz,[3] Böhm,[4] and Bary.[5] Differences in the degree of the reaction were observed by the first two authors in accordance with the strength of the barium solution employed. When small doses were given (0.01 gm.) only slight rises in the blood pressure were observed. After larger doses (0.02 gm.) the increase in the blood pressure was followed by an irregularity of the heart, while still larger amounts (0.04 gm.) caused in addition a rapid fall in blood pressure and the death of the animal. Bary corroborated these results and

[3] Mickwitz, Dissertation, Dorpat, 1874.

[4] Böhm, *Archiv f. exper. Path., u. Phar.*, 1875, iii, 216.

[5] Bary, Dissertation, Dorpat, 1888.

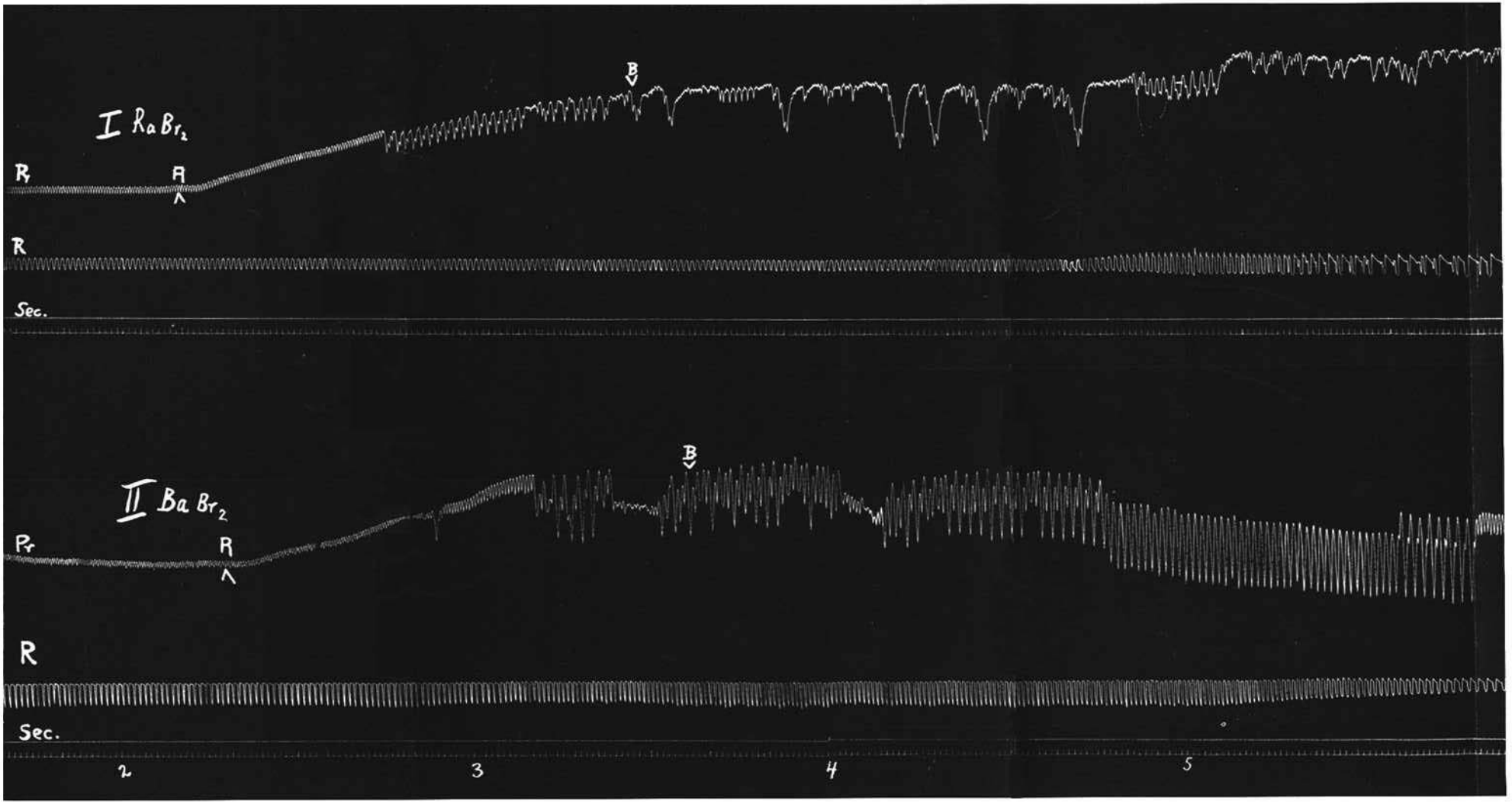
showed that the rise in blood pressure is due to a direct action of the barium upon the musculature of the blood-vessels and a slight tonic action upon the cardiac muscle.

However, in order to bring the great similarity in the action of barium bromide and radium bromide of this activity more convincingly to the attention of the reader without entering upon a lengthy description, it has been thought best to reproduce underneath Curve I a part of a tracing obtained during one of the experiments with barium. This record does not differ in any important particular from those of the other barium experiments and, moreover, on comparing it with Curve I, it would be difficult to detect fundamental points of difference in the action of these two elements.

It is entirely probable, therefore, that the effects previously attributed to the radium preparation are due in a large measure to its main constituent, barium. In accordance with this assumption we might, moreover, suppose that these circulatory and respiratory changes would be less evident after the administration of radium of higher activity, unless radium showed more markedly the effects exhibited by barium, a possibility suggested by the chemical similarity of these two elements.

To test this inference, we performed, in addition, two experiments with radium bromide of 1000 activity and four experiments with radium bromide of 10,000 activity; proportionately equal amounts of the preparation were injected.

The results derived from the experiments with the radium of 1000 activity differed practically in no way from those obtained with the radium of 240 activity. Very definite changes were observed, however, when the preparation of 10,000 activity was employed. The initial vaso-constrictor reaction lost a large share of its former conspicuousness and abruptness, while the series of short forcible contractions of the heart which often caused the blood pressure to rise suddenly in jerks beyond any ordinary level were now replaced by slow pulsations of nearly equal amplitude. The average blood pressure remained well below the normal. The most prominent symptoms, therefore, were the vaso-constriction followed shortly afterward by a marked



cardiac inhibition, but without any marked irregularity of contraction. The inhibition began during the injection of the solution and continued for an indefinite period, a complete restoration of heart action being the usual result. These effects could be produced a second and third time by renewed injections of the solution; it was found, however, that constantly larger quantities had to be used, a fact favoring the view that a certain adaptation of the body to the radium bromide does take place.

The injections were also followed by a moderate decrease in the frequency and depth of respiration, the respiratory inhibition being most pronounced during the period of cardiac inhibition. However, a complete respiratory paralysis, as in the previous experiments, did not result.

While the injections of radium bromide of 240 and 1000 activities proved fatal with only one exception, the radium bromide of 10,000 activity did not produce fatal results within the time of the experiments. It seems to be established, therefore, that the injurious effects of the radium bromide preparations used were due in a large measure to the accompanying barium salt,—at least, the evidence here brought out points to that conclusion. Naturally, complete proof of this statement can be obtained only by the use of chemically pure radium salts, i. e., such as show activities of 1,000,000 or more.