Translocation of Radioactive Silver Compounds from Site of Injection into Organs.* (24620)

HORACE GOLDIE, HAROLD D. WEST, EARL COOPER AND BERTTRAND O. TYSON
Laboratory for Experimental Oncology, Meharry Medical College, Nashville, Tenn.

We have outlined previously(1) a method for studying comparatively translocation of various radioisotopes in the mouse body. The method implied: a) subcutaneous injection of radioactive material into tails of animals, b) amputation of injected tails at various intervals, c) simultaneous autopsies in all animals, and d) counts of radioactivity in tails, blood, and some vital organs obtained by autopsies. Recently, we have applied this method in distribution studies on mice with various compounds of the same isotope, radioactive silver Ag^{111}, to provide some information on relationship between fate of an isotope in the body and physico-chemical properties of the compound into which this isotope is incorporated. Moreover, in another series of mice, some Ag^{111} compounds were injected by the same route (subcutaneously) but into a topographically different area of skin (scalp) and processed analogously (by autopsies for radioactivity). This experiment was intended to compare the effects of biological factors (topography of site of injection) on distribution.

Materials and methods. Swiss Albino male mice of 25 to 27 g weight were used. Radioactive Ag^{111} separated from palladium target and purified was obtained from Oak Ridge A.E.C. Laboratories and transformed into oxide, iodide, chloride, phosphate, and lactate.† Insoluble material was washed several times with distilled water, suspended at a ratio of 5 mc/10 cc and vigorously shaken before injection; 0.1 ml of solution or suspension was injected. A 25-gauge needle was used to inject the preparation into a thin layer of connective tissue on ventral side of the tail or subcutaneously over the scalp. Autopsies and radioactive counts were described previously (1). For interpretation comparable to previous work(1,3) we calculated the radioactivity for each mouse using radioactivity of heart blood (0.3 ml) as a standard unit. Thus, we have recorded the average pattern for each organ in each group of mice as the "organ/blood" ratio at various stages of translocation. For comparison of blood radioactivity in various groups of animals in the same experiment (series), all values in a particular series are ratios of the average radioactivity in the blood of the animals in Group 1. It should be noted that carrier-free Ag^{111} is a new product and we were unable to obtain precise information on composition of its solids; thus, in using it, we were able to give only doses of radioactivity, but not chemical doses and we realize the necessity of additional information for interpretation of our results. Nevertheless, our scouting experiments provide sufficient preliminary information for comparative trial of these compounds in tumor-bearing animals.

Results. The calculated ratios were arranged in Tables according to site of injection (Table I - Tail, Table II - Scalp) for various compounds (series) and in Table I, for various intervals (groups) between injection of radioactive compound and removal of injected tissue (*i.e.*, tail amputation). Thus, in each Table, each vertical column shows the uptake of various Ag^{111} compounds by the same organ, while each horizontal line illustrates pattern of distribution of each compound between various organs. Table II compares only with the 24 hours group in Table I.

Series A. Table I shows that injected Ag^{111} nitrate was stored in the tail during 10 minutes after injection, but within the following 50 minutes it was mostly translocated into the liver and significantly into the kidney. After 24 hours, the radioactivity pick-up in these organs remained nearly constant; blood radioactivity, which was temporarily in-

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creased, returned closely to its initial level. Distribution of the same compound 24 hours after injection into the scalp roughly resembled its pattern recorded 30 minutes after tail injection; in other terms, translocation from both sites followed the same pattern but was considerably delayed from the scalp.

Series B. During the first hour, Ag^{111} lactate was much lower than Ag^{111} nitrate in the tail and in blood whereas localization was higher in lung, kidney, and spleen. Moreover, most translocation from the tail occurred with-

TABLE I. Spread of Various Ag^{111} Compounds from Site of Injection (Tail) into Blood and Visceral Organs at Various Intervals before Removal of Injected Tissue (Tail Amputation).

Compound of Ag^{111}		Time between Ag^{111} inj. into tail and tail amputation	Radioactivity content of inj. tissue (tail) and of visceral organs expressed as ratios of avg radioactivity in same group					Comparison of blood radioactivity in different groups of same series with Group 1 as 1
Series (letters)	Groups (numbers)		Tail	Lung	Kidney	Spleen	Liver	
A. Ag^{111} nitrate								
	1	1 to 5 min.	478.4	.9	1.2	1.0	1.4	1.0
	2	10	464.1	1.2	1.1	1.1	1.2	1.6
	3	30	121.5	1.3	1.3	1.8	4.1	2.9
	4	60	96.5	2.1	1.8	1.5	8.1	3.3
	5	3 hr	84.3	1.8	2.1	1.2	7.3	2.9
	6	24	66.1	1.2	2.1	1.1	9.3	1.6
	7	48	62.1	1.6	2.2	1.1	9.8	1.3
	8	72	67.0	1.6	2.2	1.2	9.1	1.2
B. Ag^{111} lactate								
	1	1 to 5 min.	241.1	3.2	1.8	1.6	4.1	1.0
	2	10	189.4	3.1	1.3	1.4	5.9	1.3
	3	30	79.8	2.1	1.0	1.4	6.4	1.4
	4	60	49.6	1.8	1.0	1.4	8.2	1.3
	5	3 hr	41.5	1.0	1.3	1.2	10.1	2.2
	6	24	27.1	1.2	1.1	1.8	12.1	2.6
	7	48	15.9	1.7	1.4	1.5	12.3	1.2
	8	72	11.1	1.9	1.9	1.2	11.1	1.2
C. Ag^{111} oxide								
	1	1 to 5 min.	623	.9	1.0	1.2	1.2	1.0
	2	10	487	2.2	1.6	1.1	1.4	1.3
	3	30	431	1.0	.9	1.0	2.1	2.0
	4	60	390	1.1	.8	3.1	4.4	1.9
	5	3 hr	331	1.5	.9	2.2	5.9	1.3
	6	24	287	1.8	1.4	2.3	8.8	1.3
	7	48	153	3.2	1.2	2.8	9.2	1.6
	8	72	151	5.2	1.1	3.9	9.8	1.3
D. Ag^{111} chloride								
	1	1 to 5 min.	970	2.1	1.5	3.0	1.3	1.1
	2	10	790	3.2	2.8	5.3	2.1	1.3
	3	30	700	3.1	2.0	2.3	2.2	1.6
	4	60	611	2.4	2.1	4.7	4.2	1.6
	5	3 hr	510	2.5	1.4	4.8	6.4	1.2
	6	24	360	2.6	1.8	4.3	9.1	1.1
	7	48	235	6.1	2.0	4.7	9.7	1.1
	8	72	191.8	2.8	1.3	5.1	10.3	1.9
E. Ag^{111} iodide								
	1	1 to 5 min.	183	1.6	1.7	1.7	2.5	1.0
	2	10	178	2.1	1.3	1.6	3.5	1.1
	3	30	103	1.7	1.2	1.6	4.3	1.3
	4	60	81.9	1.8	1.8	1.3	4.3	1.5
	5	3 hr	61.8	1.8	1.7	1.5	5.2	1.5
	6	24	38.2	1.7	1.7	1.0	4.1	1.7
	7	48	32.2	1.6	1.7	1.1	4.4	1.4
	8	72	30.6	1.6	1.5	1.1	3.3	1.5

Ratio for each tissue is avg of 15 mice in each group.

TABLE II. Spread within 24 Hours in Body of Mouse of Silver Compounds Injected into the Scalp.

Series and compounds	Tissues and organs						Comparison of blood radioactivity in different series with Series A (in Table I) as 1
	Scalp	Periost. and bone (skull)	Lung	Kidneys	Spleen	Liver	
A. Ag^{111} nitrate	138.0	31.4	1.4	1.9	1.5	7.1	3.1
B. lactate	65.2	11.2	1.7	1.3	1.4	8.1	2.6
C. oxide	528.5	212.5	1.4	2.1	4.1	7.2	1.0
D. chloride	597.0	164.6	1.3	2.1	3.1	6.8	1.2
E. iodide	72.8	87.7	1.1	1.6	1.4	4.9	2.0

Ratio for each tissue is avg of 15 mice in each group.

in 24 hours. Translocation from the scalp during this period was about at the level of the spread from the tail after 30 to 60 minutes.

Series C and D. About one-half of Ag^{111} oxide and Ag^{111} chloride remained in the tail and much higher proportion in the scalp within at least 24 hours. Translocation of both compounds from the tail into the liver was much lower than for Ag^{111} nitrate and lactate, and it was considerably lower from the scalp; however, storage in the spleen was higher than in any other series.

Series E. As in the case of Ag^{111} lactate only a minor share of Ag^{111} iodide was stored in the tail within 10 minutes after injection and it was slowly depleted afterwards; pick-up by the liver was surprisingly low. The pattern of distribution from the scalp resembled closely that of group 5 (amputation after 3 hours) of the tail experiment.

Maxima and minima for each group varied mostly within the range of 20 to 30% of the average. In our experiments with neutral Ag^{111} phosphate, range of individual variations was much wider (due to the higher tendency of this material to clumping) and averages were not included in this report.

Discussion. Each of 5 different compounds of the same isotope showed a different pattern of dislocation from site of injection. The differences can be attributed only to variations in physicochemical properties of compounds formed by the same radioactive metal, Ag^{111}. Kyker(4) outlined very clearly a systematic approach to interpretation of various patterns in distribution of radioisotopes. He indicated that "the pH of body fluids is favorable to formation of radiocolloids when carrier free or very high specific activity material is in use"; moreover, he emphasized that "the charge, size, and chemical nature are prominent factors that influence distribution of a colloidal preparation."

Initial storage of soluble Ag^{111} compounds (Ag^{111} nitrate and lactate) at site of injection can be explained only as their fixation on tissue, tissue fluid, and blood proteins with formation of colloidal particles; their transportation in the blood and interception by liver and kidney will account for the rise of blood and liver radioactivity. For very acid Ag^{111} nitrate the combination even of low doses with blood and tissue protein resulted in a corrosive and often lethal effect. On the contrary, the weaker acid Ag^{111} lactate offered for eventual therapeutic application advantages of good tolerance by the animal and of relatively even distribution in the body.

The insoluble, coarsely particulate compounds oxide and chloride, were transported in the blood stream only slowly and in small amounts from the tail (about ⅓ remained at the site of injection after 24 hours and about 1/5 after 72 hours) and at a still lower rate (translocation of about 1/6 after 24 hours) from the scalp. The material was taken up from the blood by liver, spleen, and kidneys, and partly by reticuloendothelial elements in these organs. Previous work(5) has shown that Ag^{111} oxide was transported in connective tissue by lymphatics which became clogged by agglomeration of particles (in their lumen). This phenomenon and the presence of several large vessels in the tail may account for the higher rate of translocation from the tail. Higher tendency of Ag^{111} chloride particles to be agglutinated in tissues, perhaps

through their reaction with tissue and tissue fluid, may explain their low rate of translocation as compared to Ag^{111} oxide. Both insoluble compounds are suitable, due to their ability to be deposited and stored in requisite areas, for topical treatment of malignant conditions and perhaps also of some benign pathological tissue structures(5).

Poor vascularization and large amount of connective tissue in the scalp may account for relatively slow and scanty translocation of any compound from site of injection. Vice versa, rapid and copious translocation from the tail may be correlated with its high vascularization and low content of connective tissue.

It should be noted that according to our reports on Y^{90} chloride and Ag^{111} oxide(2,5) and our unpublished results with Ag^{111} iodide the pattern of translocation for an insoluble compound given topically was considerably modified by the presence of tumor tissue in the injected area: storage of the isotope in this area was considerably higher than in normal tissues due to occlusion of lymph channels and tissue spaces by growing malignant elements (and frequently also of blood vessels by hemorrhages). This is the rationale for therapeutic trial of above compounds in tumor-bearing mice which we are carrying out at the present time.

Summary and conclusions. 1) Data were obtained in mice on translocation of 5 radioactive silver Ag^{111} compounds at various intervals after injection into the tail by a previously described method of serial tail amputations and 24 hours after injection into the scalp. 2) Ag^{111} nitrate storage rate at site of injection was higher than for another soluble compound—Ag^{111} lactate, but lower than for 2 insoluble coarsely particulate compounds—Ag^{111} oxide and chloride; on the contrary, pick-up by liver and blood was highest for soluble compounds. 3) Translocation of each compound from the scalp followed the pattern of its translocation from the tail but at a much slower rate. 4) In the above experimental conditions the fate of various Ag^{111} compounds in the body of the mouse depended mainly a) on the physico-chemical properties of the compound (solubility, pH, ability to form colloidal complexes with tissue fluid and blood, size and tendency of insoluble particles to clump) and b) on biological conditions at site of injection. 5) The planned use of this method in tumor-bearing mice is presumed to be helpful for selection of the choice compound for local or systemic therapeutic application.

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Antihypertensive Properties of Furazolidone. (24621)

VINCENT C. DESIDERIO AND JOHN R. BEEM (Introduced by John H. Moyer)
Dept. of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

Sustained diastolic hypertension is associated with progressive decrease in renal function and increase in cardiac and cerebrovascular complications(1). Effective reduction of blood pressure arrests this progressive vascular deterioration(2). Although potent vasodepressor drugs have been developed, intolerance to certain of their actions has prolonged the search for new therapeutic agents which may obviate these difficulties(3). Differing modes of antihypertensive activity are being explored to gain insight into pathogenesis of primary hypertension, thereby affording a more rational therapeutic approach. Recent observation that blood pressure might be reduced during initial clinical pharmacologic