QUANTITATIVE DISTRIBUTION OF PARTICULATE MATERIAL (MANGANESE DIOXIDE) ADMINISTERED INTRAVENOUSLY TO THE DOG, RABBIT, GUINEA PIG, RAT, CHICKEN, AND TURTLE.

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The convenient method for manganese determination developed by Reiman and Minot (1) has been utilized by Drinker and Shaw (2) in a series of observations upon the distribution of finely divided manganese dioxide introduced intravenously in the cat. A discussion of the extensive literature upon the intravenous injection of insoluble foreign particles, together with a detailed description of the technique employed in their experiments, will be found in the latter paper. Since plans for future work have made necessary the use of other laboratory animals than the cat, and since the possibility of differences between species in the ability to clear the blood stream of foreign material has been insufficiently investigated, a similar study to that made by Drinker and Shaw (2) with the cat was undertaken with other common laboratory animals. The results are reported in the present paper.

EXPERIMENTAL.

The suspensions of manganese dioxide employed contained no particles above 1 micron in size, and on analysis varied in manganese content from 0.140 to 0.903 mg. of manganese per cc. The number of particles varied between 2.5 and 5 billion per mg. of manganese. Tissues to be analyzed were taken from the body immediately after the animal had been bled to death, and the results are expressed in milligrams of manganese per 100 gm. of wet tissue. The results of Bertrand and Medigreceanu (3), with work of Reiman and Minot (1) and with analyses made by ourselves, indicate that the normal

manganese content of the tissues reported in this paper is negligibly small. The amounts shown in Table I are of no significance in view of the comparatively large injections made—large enough to assure detection of manganese in any organs in which manganese dioxide particles lodge.

In all instances injections of manganese dioxide suspensions were made under urethane anesthesia, and in the dog and rabbit records of blood pressure and respiration show, as in the cat (2), that no toxic

TABLE I.

Average Normal Manganese Content per 100 Gm. of Wet Tissue.

Organ.	Amount of manganese per 100 gm. of wet tissue.						
	Fifteen cats.	Eight dogs.	Eight rabbits.	Two guinea pigs.	Two rats.	Two chickens.	Two turtles.
	mg.	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
Liver	0.341	0.238	0.178	0.371	0.326	0.311	0.119
Spleen	0.069	0.022	0.054				
Brain	0.035	0.044	0.062				
Stomach	0.046	0.043	0.059				
Small intestine	0.044	0.028	0.068	0.137*	0.099*	0.051*	0.061*
Colon	0.086	0.080	0.099				
Cecum and appendix			0.043				
Kidney	0.136	0.087	0.147	0.000	0.110	0.124	
Lung	0.031	0.023	0.036	0.000	0.000	0.000	0.000
Muscle	0.025	0.020	0.022	0.043	0.000	0.030	0.016
Bone			0.101				
Urine	0.000	0.000	0.000				
Blood	0.000	0.000	0.000				

* Entire intestinal tract.

symptoms attend such injections. While records were omitted during the injection of the smaller animals no unfavorable symptoms were noted.

The injected animals were killed by bleeding to death from the carotid arteries at the end of 1 hour. Organs for analysis were at once removed, weighed wet, and the manganese content was recorded in milligrams per 100 gm. of tissue. Drinker and Shaw (2) found for the cat that the liver, lungs, and spleen are the points of maximum lodgment, and our observations indicate that this is also true for

other animals. Table II shows the small amounts removed by tissues exclusive of the liver, lungs, and spleen in the rabbit. Table III presents the percentages of injected manganese deposited in the liver, lungs, and spleen of the animals employed. A column is also included, which obviously cannot be completely accurate, to represent the traces found in the blood, and a final column represents the percentage of injected material deposited in other organs than those

TABLE II.

Distribution of Manganese in Tissues Exclusive of the Liver, Lungs, and Spleen in the Rabbit after the Intravenous Injection of Manganese Dioxide.

Weight 2.6 kilos. Mar. 9, 1920. Injection of 13.6 cc. of manganese dioxide suspension containing 19.3 mg. of manganese per 100 cc. Total injection 2.62 mg. of manganese.

Organ.	Amount of manganese recovered.	Per cent of injected manganese recovered.
	mg.	
Brain	0.000	0.00
Stomach	0.000	0.00
Small intestine	0.031	1.2
Colon and rectum	0.013	0.5
Cecum and appendix	0.000	0.00
Kidney	0.007	0.3
Bone	0.004*	2.2†
Heart	0.002	0.1
Blood	0.022	0.7‡
Total	0.079	5.0

* Tibia.

† Bone weight of body calculated at 5 per cent of body weight.

‡ Blood weight of body calculated at 7 per cent of body weight.

chiefly concerned in removing foreign particles from the blood stream. The latter amount varies between 19 per cent in one guinea pig and 2 per cent in one rat. It is impossible to foretell why such variations occur and where the manganese will be found. In the rabbit even during the 1st hour following injection there is a variable degree of excretion in the bile. Some of this manganese is thus included in analyses of the duodenum and jejunum. The intestinal wall of all

the animals studied shows small and very variable amounts of deposition. The same is true of muscle and kidney.

Text-fig. 1 is a graphic representation of the data from Table III. The most striking feature of the figure is that the lungs of the cats contain practically 50 per cent of the manganese 1 hour after injection, while the lungs of all the other animals contain minute amounts, Dog 1 with 14 per cent being the single exception to this.

TABLE III.

Distribution of Manganese 1 Hour after the Intravenous Injection of Manganese Dioxide.

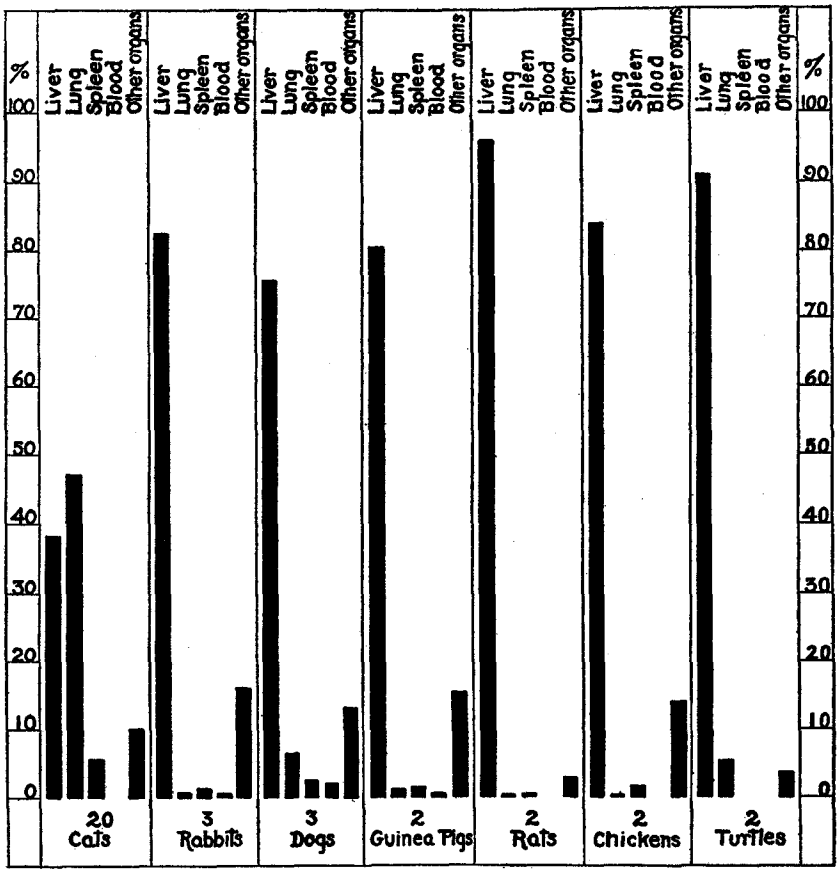
Animal.	Amount of manganese injected.	Per cent of injected manganese recovered.				
		In liver.	In lungs.	In spleen.	In blood.*	In other organs.
	mg.					
Average for twenty cats		38.3	47.0	4.7	0.0	10.0
Rabbit 1	7.98	81.0	1.2	0.8	0.6	16.5
" 2	6.18	81.0	0.2	2.5	0.7	15.4
" 3	2.71	85.6	0.52	0.55	0.0	13.3
Dog 1	83.5	64.0	14.0	2.0	3.9	16.1
" 2	45.2	83.0	3.7	2.1	2.1	9.1
" 3	67.7	79.0	2.0	4.0	0.9	14.1
Guinea Pig 1	2.03	76.0	2.1	1.7	1.2	19.0
" " 2	2.34	85.0	0.8	1.4	0.3	12.5
Rat 1	1.34	94.0	0.5	1.9	0.0	3.6
" 2	0.83	98.0	0.6	0.0	0.0	2.0
Chicken 1	4.36	84.0	0.0	1.7	0.0	14.3
" 2	2.82	84.0	0.4	1.7	0.0	13.9
Turtle 1	1.13	94.0	3.0	No analysis.	0.0	3.0
" 2	1.0	88.0	7.5	" "	0.0	4.5

* Blood weight calculated at 7 per cent of body weight.

In the animals whose lungs removed less of the suspension from the circulating blood the liver removed more manganese so that the amount scattered among the other tissues was very little greater or was even less than in the cats.

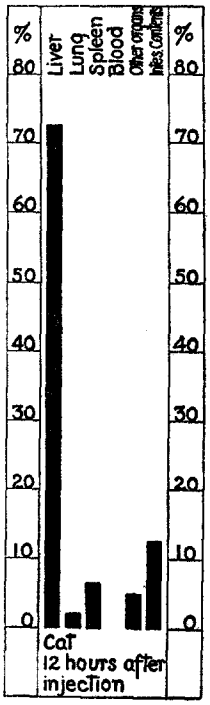
In Text-fig. 2 the distribution of manganese dioxide 12 hours after injection in the cat is shown. At this period the animal had lost the high lung concentration which was observed 1 hour after injection. The material had accumulated in the liver, from which it slowly

escaped through the bile. With the rabbit and guinea pig killed 15 minutes after injection, no difference was found in distribution of manganese dioxide from that shown in Text-fig. 1. These animals,



TEXT-FIG. 1. Distribution of manganese in the organs of animals 1 hour after the intravenous injection of manganese dioxide.

therefore, unlike the cat do not go through the stage of deposition in the lungs and final collection in the liver, but the foreign material is at once localized where its removal from the body is best accomplished.



TEXT-FIG. 2. Distribution of manganese in the organs of a cat 12 hours after the intravenous injection of manganese dioxide.

DISCUSSION AND CONCLUSIONS.

The experiments presented may be contrasted with but little other work with injected particles, since previous experimentation has lacked any quantitative basis. Voigt (4) has published a series of papers on the distribution of colloidal silver and colloidal silver iodide. He determined the distribution both chemically and microscopically. His suspensions differed from ours in several ways. In the first place, the individual particles of his suspensions were much finer, having an average diameter of 15 to 20 micromicrons in contrast to the 0.6 to 1 micron diameter of the manganese dioxide particles used in the present study. Also, the concentration of Voigt's suspensions was far greater, ranging from 10 to 50 per cent in contrast to 0.015 to 0.09 per cent in our work. Furthermore, some of his suspensions must have shown agglutination, since he found emboli in the lungs of rabbits. In spite of these differences, three rabbits, killed at a longer interval following injection than the animals in our experiments, displayed 0.2, 5.1, and 3.7 per cent of the injected material in the lungs, out of a total of 38, 89, and 63 per cent recovered on analysis of all tissues.

In the same experiments the livers contained respectively 35, 80.7, and 51.8 per cent of the material injected. These rather rough results agree with our own and confirm the indication that in the rabbit the lungs play a very minor part in clearing the blood of foreign particles.

More recently Duhamel (5) has published a brief note upon injections into rabbits of colloidal platinum, selenium, mercury, copper, and iron. On chemical analysis he found a large proportion of the injected material in the liver. Again the individual particles were very small but the function of the liver in removing them from the circulation is obvious.

It has been recognized for many years that soluble salts of the heavy metals are deposited from the blood in the liver, and that this deposition plays an important part in the removal of such salts from the body. Clearly, the organ operates with an equal degree of efficacy in the case of particles up to 1 micron in diameter, and probably would do so with even larger sizes, though as yet we have no data upon the subject.

As Drinker and Shaw (2) have discussed much of the bacteriological work relating to removal of organisms from the blood stream, it is only necessary here to mention such data as display differences between the lung element in the reaction. Bartlett and Ozaki (6), using histological methods for detection, found larger numbers of staphylococci in the lungs of dogs and rabbits killed 1 to 30 minutes after injection than in other organs. By the end of an hour fewer bacteria were detected in the lungs than in the liver and spleen. Arima (7) found few bacteria (*Staphylococcus aureus*, *B. coli*, and *B. typhosus*) in the lungs of rabbits 1 hour after injection. Kyes (8) found few pneumococci in the lungs of pigeons. These observations, with the exception of those of Bartlett and Ozaki (6), agree well with our findings in the case of manganese dioxide particles. It is only possible to express a rough opinion as to quantities of material on the basis of histological examination, and we are thus inclined to believe that the atypical results of Bartlett and Ozaki (6) represent an error in judgment and do not affect the facts of the case.

The most important and conclusive work with bacteria is that of Hopkins and Parker (9). They found a marked difference in distribution of streptococci injected intravenously into cats and rabbits. Using comparatively accurate cultural methods they found the following distribution of streptococci 10 minutes after injection.

The result is in conformity with that obtained in the present study for manganese dioxide particles of approximately the same size as streptococci. It is not known why the cat and the rabbit display these differences, but fortunately the cat is unique among the labo-

Organ.	No. of streptococci per 0.1 gm. of tissue.	
	In cat.	In rabbit.
Lung	315,000	41,000
Liver	34,000	104,000
Spleen	18,000	120,000
Kidney	100	0
Bone marrow	500	
Psoas	8	1,500
Pectoralis	27	
Blood	26	

ratory animals tested and is seldom used for bacteriological work.

SUMMARY.

The distribution of manganese dioxide particles 1 hour following intravenous injection in cats, dogs, rabbits, guinea pigs, rats, chickens, and turtles is described. This distribution is remarkably constant for all the animals tested, except the cat, in which the injected material is practically equally divided between the lungs and liver. In the other animals the liver performs the main share of the work, and in the cat it has been shown that the liver after 12 hours accumulates the manganese which was formerly deposited in the lungs.

The results are in harmony with experiments in which bacterial suspensions are employed for injection and confirm the suggestion previously made (2) that in the first handling of foreign particulate material the animal behaves similarly whether protein or inorganic injections are used.

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