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THE PENETRATION OF INORGANIC IONS THROUGH THE WALL OF A TUBERCULOUS CAVITY

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The aim of this paper is to study the penetration of sodium and bromide ions in tuberculous lung tissue, for if these ions injected into the blood stream could not in a short time penetrate the centre of a tuberculous cavity, it would probably be impossible for the much bigger streptomycin or P.A.S. molecules to do so.

We have chosen to work with sodium and bromide which are easily diffusible and have suitable radioactive isotopes for this purpose.

EXPERIMENT I

The radioactive isotopes Na^{22}, Na^{24}, and Br^{82} were given intravenously before operation to patients undergoing lung resection for pulmonary tuberculosis. Immediately after removal of the lung tissue, pieces were taken from different parts of the specimen and put in small vials and weighed. The activity was measured by scintillation counting. The background was subtracted and the activity per gram of tissue was calculated. Six thousand to 10,000 impulses were counted, and the counting errors evaluated.

The diffusion of Na^{22} and Br^{82} into different tissues was studied in seven cases undergoing operation for pulmonary tuberculosis. The result obtained with bromide was identical with that obtained with sodium. The isotopes were administered intravenously 16 to 24 hours before operation, i.e., before ligation of the vessels to that part of the lung being resected, when 2–6 microcurie Na^{22} (half-life two and a half years) or 40 microcurie Br^{82} (half-life 35 hours) were given.

It is very difficult to compare the concentration values obtained from different patients. For example, the wall of a cavity is thin in some cases and very thick in others, but in spite of such difficulties we have tried to compare the values. For this purpose we have calculated the "relative concentration," which is defined as counts per minute per gram tissue (c.p.m./g.) divided by the counts for the total dose given/weight of the patient in grams. The theoretical assumption is that the injected isotope was equally distributed in the body. The relative concentration may be expressed as

$$\frac{\text{c.p.m./g. tissue (obtained)}}{\text{total c.p.m./g. body weight (calculated)}}$$

For a given case (Table I) roughly the same concentration of sodium or bromide was found in

TABLE I

CONCENTRATIONS OF Br^{82} AND Na^{22}

Case No.:	1	2	3	4	5	6	7
Injected isotope	Br^{82}	Br^{82}	Br^{82}	Na^{22}	Na^{22}	Na^{22}	Na^{22}
Time of lung resection after injection	17 hours	16 hours	17 hours	24 hours	24 hours	18 hours	17 hours
	Rel. conc.	Rel. conc.	Rel. conc.	Rel. conc.	Rel. conc.	Rel. conc.	Rel. conc.
Centre of a tuberculous cavity			2·7±0·09				
Wall of a cavity		2·2±0·08	2·4±0·09				
Tuberculoma	1·2±0·01	1·5±0·04		1·6±0·27			
Normal lung		2·3±0·08	1·5±0·06		2·7±0·54		
Bronchus		1·9±0·09				1·6±0·14	
Thickened pleura		2·4±0·06			2·1±0·21		0·8±0·03
Skin						0·8±0·05	0·9±0·08
Rib							0·7±0·06
Hilar lymph node					2·9±0·22		
Blood					2·7±0·19	0·7±0·02	0·5±0·03
Atelectatic lung	1·5±0·02	2·3±0·09		1·5±0·12	2·9±0·22	0·9±0·04	

(1) the normal lung tissue, (2) the wall of a tuberculous cavity, (3) the centre of a tuberculous cavity, (4) a tuberculoma, (5) a bronchus, (6) a rib, (7) the skin, (8) a hilar lymph node, and (9) the thickened pleura.

This investigation thus showed that the available sodium or bromide space is roughly the same in tuberculous lung tissue as in normal tissue when measured 16 to 24 hours after the injection of Na^{22} or Br^{82}.

Although there are very few vessels in the wall of a tuberculous cavity, the tagged sodium or bromide was found in the centre of the cavity in the same concentration as in the surrounding lung tissue. The penetration through this relatively avascular tuberculous tissue must therefore be considerable.

Experiment II

From a clinical point of view it was considered interesting to see if penetration through tuberculous tissue was retarded when compared with penetration in normal lung tissue.

The normal distribution curve of Na^{24} (half-life 15 hours) between blood and normal lung tissue was investigated in the following manner. The right chest was opened in a dog and Na^{24} injected intravenously. Then blood samples were taken at intervals from a catheter in the right atrium, and at the same time a biopsy was taken from the right lung. The concentration of Na^{24} in lung tissue and blood followed each other, which was expected as lung tissue contains a capillary network. After 10 minutes the concentration curve had levelled off (Fig. 1 and Table II).

The form of the concentration curve must be different in different tissues according to the different rates of penetration; therefore, the concentration of Na^{24} in tuberculous tissue and in normal lung tissue was compared in six

Table II

NORMAL CONCENTRATIONS OF Na^{24} AFTER INTRAVENOUS INJECTION IN DOGS

Time after Intravenous Injection of Na^{24}	Concentration in Blood (c.p.m./g.)	Concentration in Lung Tissue (c.p.m./g.)
0 min.	3± 2·6	45±109
5 ,,	1,945±16·5	3,342±206
10 ,,	1,526±12·2	1,682±84·7
15 ,,	1,385±11·2	1,970±120
1 hour 15 min.	823± 7·1	1,019± 67

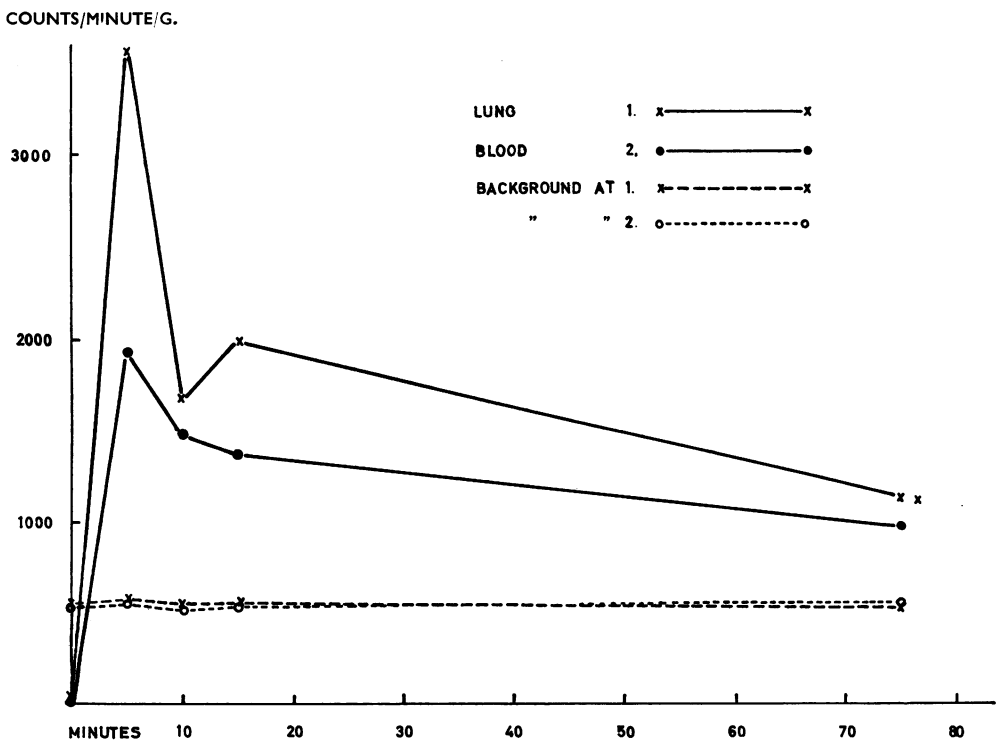

FIG. 1.—The concentration curve of Na^{24} in blood and normal lung tissue of a dog after intravenous injection.

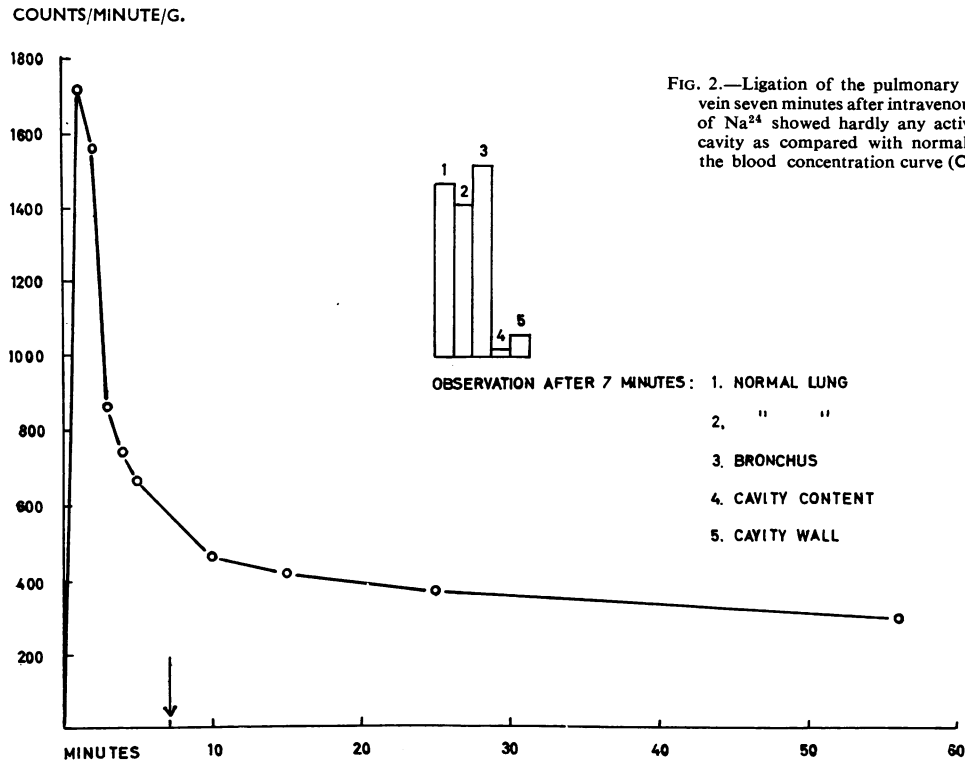

FIG. 2.—Ligation of the pulmonary artery and vein seven minutes after intravenous injection of Na^{24} showed hardly any activity in the cavity as compared with normal lung and the blood concentration curve (O- - - - O).

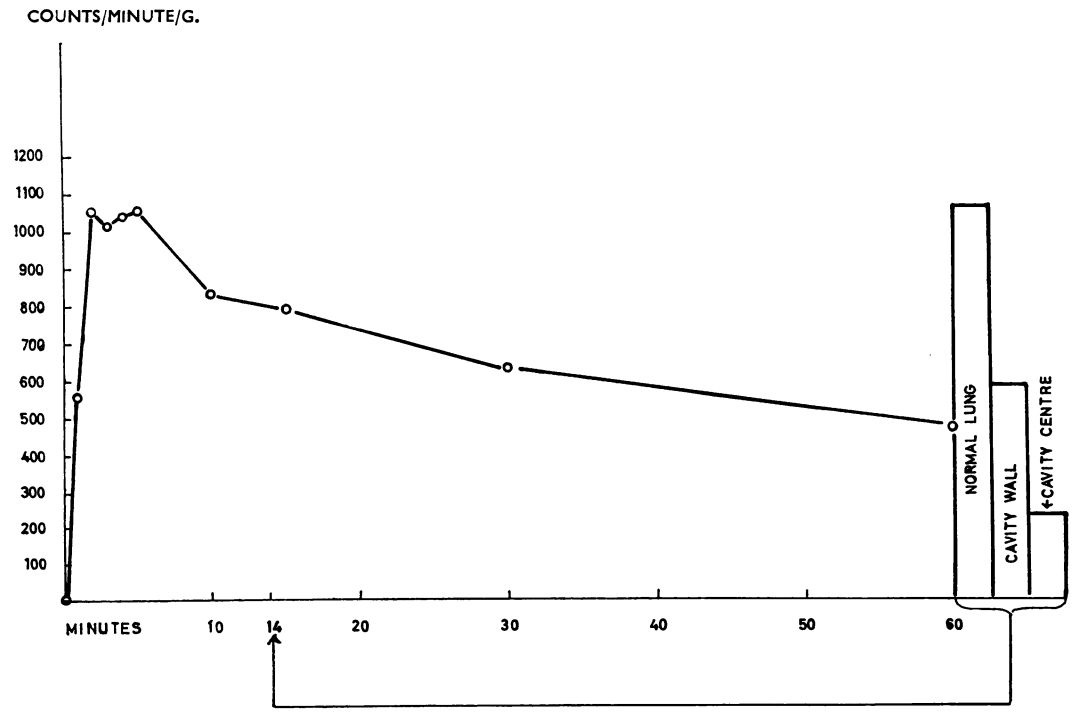

FIG. 3.—Fourteen minutes after the injection of Na^{24} a significant diffusion to the tuberculous cavity was observed.

TABLE III
CONCENTRATION OF Na^{24} IN TUBERCULOUS AND NORMAL LUNG TISSUE

Case 8		Case 9		Case 10		Case 11		Case 12		Case 13	
Ligation of the Pulmonary Vessels 7 min. after i.v. Injection of Na^{24} (Fig. 2)		Ligation of the Pulmonary Vessels 14 min. after i.v. Injection of Na^{24} (Fig. 3)		Ligation of the Pulmonary Vessels 30 min. after i.v. Injection of Na^{24} (Fig. 4)		Ligation of the Pulmonary Vessels 30 min. after i.v. Injection of Na^{24}		Ligation of the Pulmonary Vessels 1 Hour after i.v. Injection of Na^{24}		Ligation of the Pulmonary Vessels 2 Hours after i.v. Injection of Na^{24}	
Tissue	Rel. Conc.	Tissue	Rel. Conc.	Tissue	Rel. Conc.	Tissue	Rel. Conc.	Tissue	Rel. Conc	Tissue	Rel. Conc.
Blood 0 min.	—	Blood 0 min.	—	Blood 0 min.	—						
Blood 1 min.	47·1 ± 0·53	Blood 1 min.	1·6 ± 0·02	Blood 1 min.	11 ± 0·12						
Blood 2 min.	9·7 ± 0·12	Blood 2 min.	3·7 ± 0·04	Blood 3 min.	6·5 ± 0·09						
Blood 3 min.	7·6 ± 0·10	Blood 3 min.	3·6 ± 0·04	Blood 5 min.	5·0 ± 0·22						
Blood 4 min.	6·6 ± 0·09	Blood 4 min.	4·0 ± 0·04	Blood 10 min.	3·6 ± 0·16						
Blood 5 min.	6·1 ± 0·09	Blood 5 min.	3·7 ± 0·04	Blood 15 min.	3·2 ± 0·06						
Blood 10 min.	4·1 ± 0·06	Blood 10 min.	2·9 ± 0·04	Blood 30 min.	2·7 ± 0·06						
Blood 15 min.	3·7 ± 0·07	Blood 15 min.	2·7 ± 0·03	Blood 66 min.	2·2 ± 0·04						
Blood 25 min.	3·4 ± 0·06	Blood 30 min.	2·2 ± 0·03	Blood 103 min.	2·2 ± 0·05	Hilarlymph node	2·5 ± 0·02			Thickened pleura	2·8 ± 0·05
Blood 56 min.	2·6 ± 0 05	Blood 60 min.	1·7 ± 0·03	Blood 135 min.	1·8 ± 0·04	Muscle	0·7 ± 0·04				
Centre of a cavity	0·5 ± 0·08	Centre of a cavity	0·8 ± 0·15	Centre of a cavity	1·1 ± 0·19	Centre of a cavity	2 6 ± 0·03	Centre of a cavity	3·1 ± 0·002	Centre of a cavity	3·1 ± 0·27
Wall of a cavity	0·03 ± 0·03	Wall of a cavity	0·9 ± 0·05	Wall of a cavity	3·3 ± 0·48	Wall of a cavity	1·3 ± 0·06	Wall of a cavity	3·4 ± 0·005	Wall of a cavity	2·3 ± 0·01
Normal lung	3·6 ± 0·11	Normal lung	3·8 ± 0·17	Normal lung	2·6 ± 0·14	Normal lung	1·7 ± 0·06	Normal lung	3·5 ± 0·005	Normal lung	2·5 ± 0·05
Bronchus	4·6 ± 0·14							Bronchus	3·4 ± 0 006	Bronchus	5·5 ± 0·02

different clinical experiments, where the Na^{24} was allowed to circulate in the blood for seven, 14, 30 minutes, one hour, and two hours. Also in the first three cases (Cases 8, 9, and 10) the concentration curve in blood was determined from blood samples taken at intervals from the right atrium.

After seven minutes (Case 8, see Fig. 2 and Table III) no significant amount of activity was found in the wall of a tuberculous cavity (4.4 ± 12 counts/min./g. or c.p.m.) and a very little activity in the detritus in the central part of the cavity (57 ± 13 c.p.m./g.). At the same time there was a significant activity in the blood (688 ± 10 c.p.m./g.), in normal lung tissue (407 ± 13 c.p.m./g.), and in bronchial tissue (516 ± 15.5 c.p.m./g.).

After 14 minutes (Case 9, see Fig. 3 and Table III) there was already significant activity in the wall of the cavity (567 ± 33) as well as in the detritus in the centre of the cavity (216 ± 41). At the same time the activity in normal lung tissue was $1{,}071 \pm 47$, or about double the activity found in the wall of the tuberculous cavity.

In a third patient (Case 10, see Fig. 4 and Table III) the resection was made 30 minutes after the injection of Na^{24}. Significant activity was then found in the wall of the cavity (398 ± 58 c.p.m./g.). Detritus from the centre of the cavity showed much less but still significant activity, i.e., 126 ± 23 c.p.m./g. At the same time normal lung tissue showed an activity of the same magnitude as that in the wall of the cavity, i.e., 316 ± 18 c.p.m./g.

The additional three cases which were studied 30, 60, and 120 minutes after the injection of a radioactive isotope gave the results shown in Table III. The penetration of sodium ions into the normal lung and the centre of a cavity (Cases 8–13) is shown in Fig. 5.

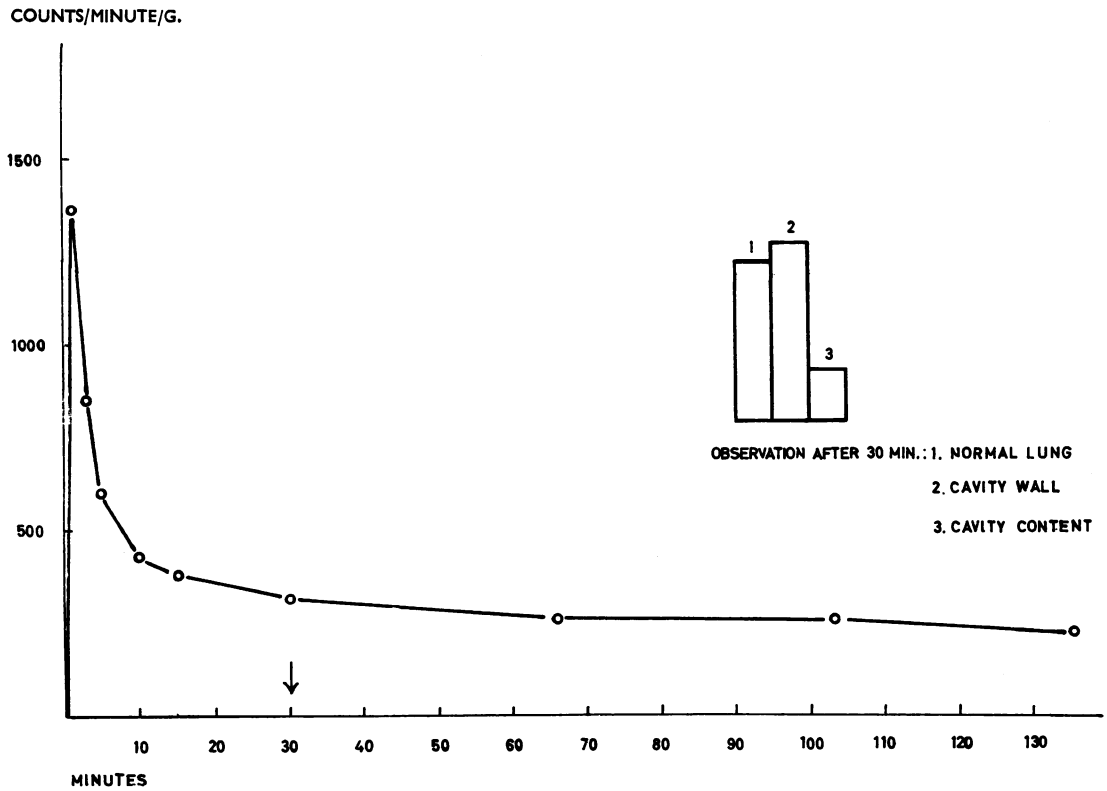

FIG. 4.—Thirty minutes after injection of Na^{24} a significant concentration in the cavity wall and cavity content was observed.

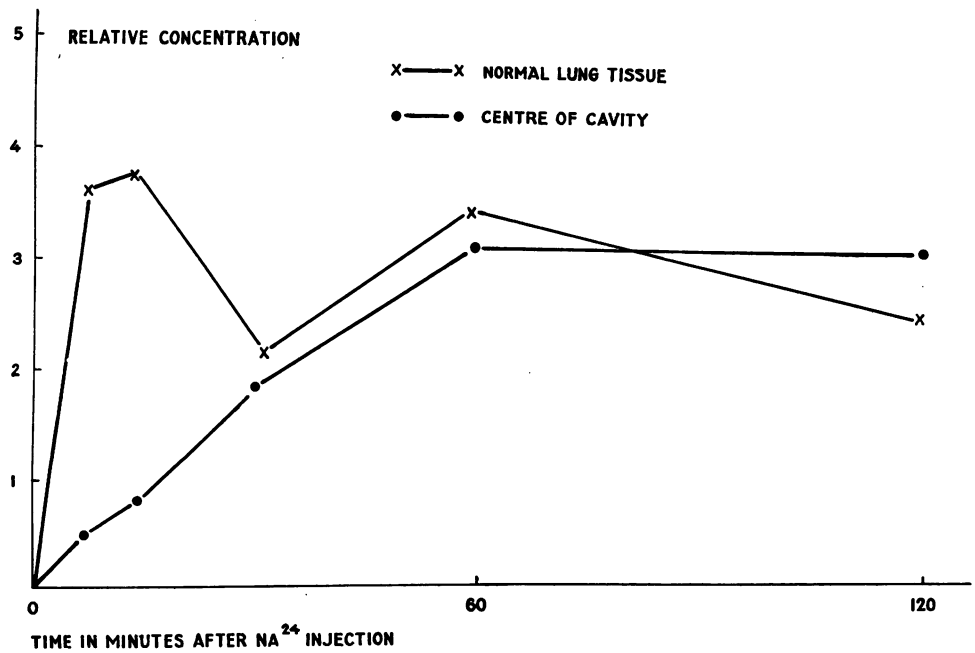

FIG. 5.—The penetration of sodium ions into the normal lung and the centre of a tuberculous cavity. Resection is performed at different intervals after intravenous injection of Na^{24} (Cases 8–13).

It has thus been found that the activity of Na^{24} in normal lung tissue after an intravenous injection is parallel to the blood concentration of that substance in experiments in dogs.

As shown in Table III and Fig. 5, the penetration of sodium ions into a tuberculous cavity of moderate size takes place at an easily measurable rate and is slower than the penetration into lung tissue. After about one hour the concentration reached the maximal value. These results indicate that the rate of penetration of the bigger molecules of therapeutic drugs may be of the order of hours. This question will be studied in further experiments.

Our results also give some information on the rate of exchange metabolic products such as oxygen and carbon dioxide in cavernous tissue as the molecular weights are comparable with that of sodium. This question will also be examined in more detail.

Summary

Na^{22}, Na^{24}, and Br^{82} were first used to demonstrate that the sodium space was the same in tuberculous tissue as in normal lung tissue when measured 24 hours after injection. Na^{24} was used to demonstrate the speed of diffusion through the wall of a cavity.

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