THE DISTRIBUTION OF RADIOACTIVE IODINE (I-131) IN EXPERIMENTAL COCCIDIOIDOMYCOSIS AND SPOROTRICHOSIS*

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Iodine and its compounds have been used on an empirical basis in the treatment of various infectious diseases for many years. Its therapeutic efficacy in the past has been recorded in such diseases as the gumma of syphilis (1), North American blastomycosis, chromoblastomycosis and cryptococcosis (2). Iodides are still recommended as specific therapy in sporotrichosis and their administration causes rapid improvement (3).

Iodides have been noted to have an adverse effect on the course of tuberculosis (4) and in some cases of North American blastomycosis (2). Two theories have been advanced to explain these adverse effects. The first is that iodides "dissolve" the fibrous tissue capsule which acts as a barrier in preventing dissemination of the infectious organism (4). The second theory is that the destruction of large numbers of organisms as the result of administration of iodides releases breakdown products which have a toxic effect on the patient (5).

Although the exact site and modality of action of iodine is still speculative, the majority of investigators are of the opinion that iodine has little direct effect on the organism but modifies the host's response to the parasite. Skinner et al (6) cite evidence that *Sporotrichum schenckii* survives in media containing a 10 per cent concentration of potassium iodide. They state that the therapeutic effect of iodides is due to their ability to stimulate the formation of fibrous tissue which tends to wall off the organisms. Jobling and Petersen (7) in a comprehensive study reviewed the early literature regarding the modality of action and proposed a theory which has received wide acceptance. They postulated that normally there are present in the blood and tissue enzymes or ferments which play an important part in the autolysis of necrotic tissues, tubercles and gummas. They found that these enzymes were rendered inactive by certain fatty acids present in the blood and in tuberculous caseous matter. They postulated that the therapeutic value of iodine was due to its ability to combine with the unsaturated fatty acids of the body and as a result lower the antitryptic (antienzyme) strength of the serum and of the tissues in general and permit the removal of dead matter by autolysis.

Burke (8) in discussing the role of iodine in the treatment of syphilis felt that the predominantly lipoidal chemical character of the spirochete caused the production of excessive deposits of fibrous tissues and that this lipoid material also interfered with certain autolytic ferments of the blood which have the property of inhibiting the formation of such excessive fibrous tissue. He further stated that this neutralization was, in the main, due to the unsaturated lipoid radicals in the lipoid-rich material of the spirochete and that the therapeutic value of iodine was due to its ability to combine with these unsaturated lipoid radicals. Once the spirochetal lipoids are saturated they are no longer able to combine with enzymatic regulators of fibrin production and thus excessive fibrous tissue formation is prevented and the absorption of granulation tissue takes place. Irwin (9) discussed this point and sug-

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gested that iodine was not germicidal but influenced metabolism by affecting the production of thyroxin. A recent survey among approximately 20 outstanding students of tuberculosis regarding the action of iodine on that disease emphasized the fact that there is little satisfactory information on the subject (10).

A number of investigators have presented evidence that iodine is deposited in gummatous, tuberculous and suppurative tissues in concentrations exceeding that found in corresponding normal tissues. In 1907 Loeb and Michaud (11) inoculated tubercle bacilli into one eye of each of four rabbits. The infection was allowed to develop and potassium iodide was administered. Six hours later the animals were sacrificed. The iodine concentration was determined in the various infected and corresponding normal organs. They found that the infected eyes contained 1½ to 2¾ times as much iodine as the normal eyes. In those animals in which the lungs were also involved, iodine was found in a higher concentration in the tuberculous caseous tissue than in the normal lung. Wells and Hedenburg (12) cite Loeb as making the solitary observation that the pus in a turpentine abscess contained a larger proportion of iodine than the blood itself. Later Loeb (11) analyzed the iodine content of enlarged lymph glands removed from a syphilitic patient who had been under potassium iodide treatment for a number of days. He found that the iodine concentration in the glands was six times that of the blood. Wells and Hedenburg (12) repeated and extended the experiments of Loeb and Michaud. They found that at 6, 24, 42, and 78 hours after injection the concentration of iodine in tuberculous tissue was greater than in most other tissues except the thyroid and the kidney. The amount of iodine present, however, was never as great as that found in the blood. It was further pointed out that the concentration was greater in the caseous matter than in the cellular periphery of the tubercle. Wells and Hedenburg (12) also found that the tuberculous eyes of rabbits contained more iodine than the control eyes 4, 6, and 8 hours after the injection of iodine. The amount present at 12 hours, however, was too minute to analyze. It was their feeling that the higher concentration of iodine observed in tuberculous tissues was not dependent upon any specific character of the tubercle itself; and they pointed out that other necrotic tissues also took up more iodine than normal tissues. They explained their findings by stating that normal cells, excepting perhaps kidney cells, are not perfectly permeable to iodine and lose this impermeability when killed or injured, thus becoming entirely permeable for crystalloids present in the surrounding fluid. As the iodine concentration in the blood increases and decreases with absorption and elimination, so the iodine in the necrotic areas, whether tuberculous or otherwise, varies. This indicated to them the absence of any chemical or physical binding of the iodine in such tissues.

Fujisawa, cited by Wallace and Brodie (11), also repeated the experiments of Loeb and Michaud. He also found an increased iodine concentration in tuberculous eyes and lungs but concluded that there was no specificity of iodine to tuberculous tissues as he found an increased concentration in eyes infected with streptococci and the testicular tissues of rabbits with syphilis. Wallace and Brodie (11) injected potassium iodide or potassium thiocyanate into tuberculous guinea pigs and intravenously into tuberculous and control monkeys and sacrificed the animals within three hours. They also administered potassium iodide orally daily for five days to syphilitic and control rabbits. The iodide, thiocyanate and chloride concentration was then determined in the normal, tuberculous, and syphilitic tissues, and in peritoneal transudates and compared to the concentration found in the blood and the serum. They concluded that in pathological tissues the iodine is distributed similarly to its distribution in normal tissues. It was their belief that the iodine was not in physical or chemical union within the cells, but was present as iodide in the interstitial fluid. The greater concentration of iodine which they found in pathological tissues was explained as being due to a greater proportion of extracellular fluid in these tissues. They found that the distribution of iodine corresponded to that of chloride and thiocyanate and cited this as evidence against any specific property of iodine to concentrate in granulomas.

As previously mentioned, some investigators have stated that iodine may influence infectious diseases by modifying thyroid metabolism. The function of the thyroid gland has

not been evaluated in infectious states. It has, however, been studied in numerous other stress situations. The criterion of function most commonly employed has been the ability of the thyroid gland to concentrate I-131. The mouse and the rat have been utilized in the majority of these experiments. Relatively acute stress situations such as heat (13), cold (14), nephrectomy, sham-operation, and traumatized gut (15), anoxic anoxia (15, 16), tourniquet shock (17), forced exercise and spinal cord transection (18), and injections of formalin (18, 19) have consistently been found to decrease the ability of the thyroid gland to concentrate radioactive iodine.

Stress situations of a more prolonged nature, particularly starvation, have yielded equivocal results to date. Williams et al (14), employing rats, found that fasting the animals for three days was associated with a subnormal concentration of I-131 in the thyroid gland. Meites and Wolterink (20) also found a decreased uptake of radioactive iodine by the thyroid glands of rats during starvation. They did not, however, conclude that this was the result of diminished thyroid function but pointed out the reduction in thyroid activity in starvation in rats was proportional to the reduced body weight of these animals. They stated that thyroid activity appeared to remain relatively unchanged when it was computed on a body weight basis.

Recently Catz et al (21) investigated the effect of starvation over a 24-hour period on the ability of the thyroid gland of rats to concentrate I-131. They administered the radioactive iodine immediately prior to the starvation period and found an increased amount of I-131 in the thyroid gland at the end of 24 hours. Two rats in addition were subjected to 24-hour starvation before the injection of radioactive iodine and the starvation was continued for another 24 hours. There was also an increased amount of I-131 in the thyroid of these rats. It was the opinion of the authors that these findings were the result of an acute dietary iodine deficiency and they were unable to explain the differences between their findings and those of previous investigators.

Various theories have been advanced to explain the change in thyroid activity during stress. It has been hypothesized that there is a shift of hormone activity in the adenohypophysis with augmented adrenocorticotropic hormone secretion occurring at the expense of thyrotropic hormone (22). It has also been shown that cortisone and ACTH depress thyroid function directly (23–27).

PURPOSE

The present report deals with:

1. The concentration of radioactive iodine in the thyroid gland of mice with coccidioidomycosis and sporotrichosis 24 and 48 hours after the administration of I-131.

2. A measurement of the amount of radioactive iodine present in the local granulomatous lesions of the same two diseases at 12, 24, and 48 hours after the administration of I-131.

3. A measurement of the amount of radioactive iodine present in the local granulomatous lesions of the same two diseases after administering a mixture of I-127 and I-131 daily for a 4-day period.

MATERIALS AND METHODS

1. Virgin female CCI strain mice were used throughout. The weight of all mice used was above 20 gm. and the variability in weights among the mice in each experiment was less than 4 gm.

2. Coccidioidomycosis was produced by the intraperitoneal injection of 0.1 cc. of a heavy suspension of spherules of *Coccidioides immitis*. Preparation of the

suspension of spherules for intraperitoneal inoculation has been previously described (28).

3. The inoculum of *Sporotrichum schenckii* was prepared in the following manner. *S. schenckii* was cultured at room temperature on Difco Sabouraud's dextrose agar (R) until a colony approximately 1.5 cm. in diameter was obtained. The colony was then separated from the agar substrate, placed in 10 cc. of sterile isotonic saline and ground to a fine particle size in a Tenbrock tissue grinder. Each mouse was injected intraperitoneally with 0.1 cc. of this material to produce sporotrichosis.

4. Random mice so infected were sacrificed at appropriate intervals to evaluate the course of the disease. Well-developed intraperitoneal granulomas involving and replacing the greater omentum were present in approximately 10 days in those mice with coccidioidomycosis and approximately 25 days in the mice with sporotrichosis.

5. Carrier free I-131 was prepared for Experiments I and II by dissolving its sodium salt in sterile isotonic saline so that there were 250 μc./cc. The mixture of I-127 and I-131 was prepared by dissolving the sodium salt of I-131 in sterile isotonic saline so that there were 100 μc./cc. Sodium salt of I-127 was then added to this solution so that there was 50 mg./cc.

TABLE I

*Radioactive iodine (I-131) uptake by the thyroids of mice with coccidioidomycosis and controls at 24 and at 48 hours**

Mouse Number	24 Hours		48 Hours	
	Control mice	Infected mice	Control mice	Infected mice
1	234	189	290	144
2	156	139	175	129
3	323	126	146	28
4	186	168	249	114
5	185	66	109	33
6	165	147	148	112
7	169	99	81	98
8	196	52	202	134
9	292	112	42	30
10	140	168	197	112
Mean	205	127	164	93
Standard deviation	±60.29	±44.69	±75.26	±50.2
Standard error of the difference between the two means				
	3.1		2.3	
Significance (P)				
	516:1		54.6:1	

* Recorded in counts/second/gm of animal at the time of death.

One-tenth of a cubic centimeter of these solutions was injected subcutaneously into the back of each mouse. A 0.25 cc. graduated tuberculin syringe and a 1.5 cm 27-gauge needle were used for this purpose. The degree of radioactivity of the various tissues was determined with a sodium iodide scintillation counter (29). The amount of radioactivity of the tissues except for the thyroid gland is computed and recorded as counts/second/gm. of tissue. In the case of the thyroid gland, radioactivity is computed and recorded as counts/second/gm. of body weight of the animal at the time of death.

EXPERIMENT I

The Determination of Radioactive Iodine in the Thyroid Gland of Mice with Coccidioidomycosis and Sporotrichosis at 24 and 48 Hours after the Administration of I-131

Part 1. Twenty mice were inoculated with *C. immitis* as described above and 20 matched mice were used as controls. Seven days later 25 μc of I-131 was given subcutaneously to all mice. Twenty-four hours later 10 infected and 10 control mice were weighed and sacrificed. The thyroids were removed by block dissection, placed in 1-ounce ointment tins 1⅞ inches in diameter, and their radioactivity was determined by means of gamma counting. The remaining 10 infected and 10 control mice were sacrificed at 48 hours. Their thyroids were removed and evaluated for radioactivity in a similar manner.

TABLE II

*Radioactive iodine (I-131) uptake by the thyroids of mice with sporotrichosis and controls at 24 and at 48 hours**

Mouse Number	24 Hours		48 Hours	
	Control mice	Infected mice	Control mice	Infected mice
1	463	262	379	245
2	263	229	160	90
3	318	227	239	220
4	366	84	161	109
5	367	187	421	99
6	202	255	509	290
7	400	165	211	167
8	366	68	256	176
9	296	160	293	79
10	368	156	267	91
Mean	341	179	290	157
Standard deviation	±73.8	±66.6	±114.2	±79.6
Standard error of the difference between the two means				
	5.0		2.9	
Significance (P)				
	>15,000:1		267:1	

* Recorded in counts/second/gm of animal at the time of death.

Part 2. Twenty mice were inoculated with *S. schenckii* as described above and 20 matched mice were used as controls. Twenty-one days later 25 μc of I-131 was given subcutaneously to all mice. Ten controls and 10 infected mice were sacrificed at 24 hours and a similar group at 48 hours. Their thyroids were removed and the radioactivity was determined as in Part 1.

Results of Experiment I

Tables I and II summarize the data obtained from experiment I, parts 1 and 2. These indicate that the thyroid glands of the noninfected mice concentrate significantly more I-131 at 24 and 48 hours than the thyroid glands of the mice with coccidioidomycosis and sporotrichosis.

TABLE III

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with coccidioidomycosis and comparative tissues of control mice at 12 hours**

Mouse Number	Omentum		Liver	
	Control	Granulomas	Control	Infected
1	60.8	1894.0	82.6	610.5
2	34.8	57.1	35.8	15.9
3	19.3	34.5	25.5	21.0
4	8.3	161.5	13.5	697.0
5	18.1	40.7	17.0	22.3
6	15.4	634.6	23.6	192.9
7	143.2	1022.0	195.0	587.1
8	115.2	179.8	104.5	74.2
9	2.1	295.9	8.7	149.3
10	13.2	174.3	25.2	73.3
11	3.4	1363.0	7.3	640.4
12	80.8	735.3	93.7	229.7
13	6.1	94.5	15.4	23.4
14	6.6	128.3	13.4	67.8
15	106.2	832.2	78.0	298.6
16	11.5	46.3	31.0	16.2
17	23.5	236.8	16.9	50.4
18	43.0	2525.0	44.6	886.4
19	20.8	801.2	26.7	61.2
20	4.4	36.6	11.0	24.8
Mean	36.8	564.8	43.4	237.1
Standard deviation	±40.0	±762.0	±45.4	±274.3
Standard error of the difference between the two means				
	3.1		3.1	
Significance (P)				
	516:1		516:1	

* Recorded in counts/second/gm of tissue.

EXPERIMENT II

The Determination of Radioactive Iodine in the Granulomatous Lesions of Coccidioidomycosis and Sporotrichosis at 12, 24, and 48 hours after the Administration of I-131

Part 1. Twenty mice were inoculated with *C. immitis* as described above and 20 matched mice were used as controls. Ten days later 25 μc of I-131 was given subcutaneously to all mice. Twelve hours later all mice were sacrificed. A portion of the liver and the greater part of the granulomatous large omentum was removed in each of the infected mice. Similar portions of the liver and the greater omentum were removed from each control animal. Tissues of approximately the same weight were obtained to minimize errors in the determina-

TABLE IV

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with coccidioidomycosis, and comparative tissues of control mice at 24 hours**

Mouse Number	Omentum		Liver	
	Control	Granulomas	Control	Infected
1	24.0	1959.0	62.2	1190.0
2	92.0	450.2	154.0	391.0
3	8.9	16.3	25.0	13.1
4	10.3	573.0	24.6	12.6
5	13.1	2170.0	46.5	825.0
6	23.9	1710.0	75.3	683.0
7	164.7	259.0	195.0	576.0
8	13.3	967.0	31.0	26.8
9	19.8	1380.0	71.1	282.0
10	26.4	1140.0	42.8	247.0
11	7.2	144.0	25.2	10.9
12	9.3	319.0	32.3	51.5
13	10.8	934.0	39.3	226.0
14	32.0	261.0	71.5	82.5
15	13.9	907.0	34.4	358.0
16	41.6	664.0	82.5	253.0
17	52.6	195.0	101.0	17.2
18	98.4	1780.0	141.0	917.0
19	14.3	410.0	37.0	119.0
20	15.8	1685.0	48.1	330.0
Mean	34.6	896.1	67.0	330.6
Standard deviation	±17.4	±684.0	±56.1	±325.2
Standard error of the difference between the two means	5.6		11.3	
Significance (P)	>15,000:1		>15,000:1	

* Recorded in counts/second/gm of tissue.

tion of radioactivity which might be produced by gross variations in size. The tissues were then placed in previously weighed ointment tins as described above. The tins were then reweighed to obtain the weight of the excised tissue and radioactivity was determined.

Identical experiments were performed with similar groups of 20 infected and 20 control mice in which the animals were sacrificed at 24 hours and at 48 hours after the administration of I-131. The radioactive iodine was administered on the fourteenth post-inoculation day in that group of mice which was sacrificed at 24 hours. It was administered on the seventh post-inoculation day in that group which was sacrificed at 48 hours.

Part 2. The experiment described in Part 1 of Experiment II was repeated employing *S. schenckii* as the infectious organism. The I-131 was administered on the nineteenth day after the inoculation of *S. schenckii* in the group which was sacrificed at 12 hours, the twenty-sixth

TABLE V

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with coccidioidomycosis and comparative tissues of control mice at 48 hours**

Mouse Number	Omentum		Liver	
	Control	Granuloma	Control	Infected
1	14.2	22.8	31.4	16.9
2	21.7	19.3	33.0	9.0
3	10.4	26.1	32.8	10.6
4	22.6	3.5	25.6	8.7
5	9.9	11.7	31.4	57.0
6	6.1	2.5	19.8	16.5
7	10.8	22.6	41.3	8.1
8	3.4	112.2	8.5	12.7
9	17.7	6.0	49.7	6.8
10	0.0	77.7	5.0	19.9
11	19.4	8.0	48.6	14.0
12	17.0	21.4	38.2	8.1
13	5.8	13.6	19.5	2.8
14	20.4	18.6	41.3	15.8
15	17.7	108.2	61.5	5.0
16	17.9	7.1	35.2	7.5
17	4.7	23.1	17.6	21.6
18	9.3	12.5	36.4	8.1
19	13.9	10.5	32.4	19.4
20	21.6	7.4	56.8	9.4
Mean	13.3	26.7	33.3	13.9
Standard deviation	±16.5	±32.3	±14.4	±11.1
Standard error of the difference between the two means				
	2.0		4.9	
Significance (P)				
	21:1		>15,000:1	

* Recorded in counts/second/gm of tissue.

post-inoculation day in that group which was sacrificed at 24 hours, and the twenty-seventh post-inoculation day in that group which was sacrificed at 48 hours.

Results of Experiment II

Tables III, IV, and V summarize the data obtained from Part I of Experiment II. These indicate that at 12, 24, and 48 hours the granulomatous lesions of coccidioidomycosis contain significantly more radioactive iodine per gram of tissue than comparative tissues of control mice. The concentration of I-131 in the granulomatous tissue as compared to the control tissue was greatest at 24 hours (approximately 28:1). At 12 and 24 hours the infected livers contained

TABLE VI

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with sporotrichosis and comparative tissues of control mice at 12 hours**

Mouse Number	Omentum		Liver	
	Control	Granuloma	Control	Infected
1	331	194	372	167
2	527	313	625	214
3	318	452	262	248
4	204	352	202	326
5	689	108	692	53
6	281	153	263	122
7	81	586	50	512
8	270	305	305	64
9	131	396	193	136
10	164	129	192	110
11	89	146	75	115
12	83	629	78	101
13	95	16	169	17
14	284	20	321	22
15	97	27	100	22
16	113	50	117	97
17	306	12	599	11
18	569	82	363	64
19	239	61	220	479
20	314	202	155	171
Mean	259	212	268	153
Standard deviation	±133	±184	±179	±137
Standard error of the difference between the two means	0.92		2.2	
Significance (P)	2:1		35:1	

* Recorded in counts/second/gm of tissue.

significantly more I-131 per gram of tissue than the livers of the control mice. These findings were reversed at 48 hours; that is, the concentration of I-131 in the control livers was greater than in the livers of the infected mice.

Tables VI, VII, and VIII summarize the data obtained from Part 2 of Experiment II. These indicate that there is no significant difference between the concentration of I-131 in the granulomatous lesions of mice with sporotrichosis and the comparative tissues of control mice at 12 and 24 hours. The granulomatous tissue, however, does contain a significantly greater amount of I-131 at 48 hours. The concentration of I-131 in the livers of the control mice was greater than the livers of the mice with sporotrichosis at 12 and 24 hours. There was no significant difference between the livers of the infected and control mice at 48 hours.

TABLE VII

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with sporotrichosis and comparative tissues of control mice at 24 hours**

Mouse Number	Omentum		Liver	
	Control	Granuloma	Control	Infected
1	34.2	39.4	72.9	23.2
2	8.3	38.6	15.2	24.4
3	12.3	12.9	18.5	11.0
4	12.5	22.1	40.5	35.7
5	8.8	24.8	25.2	29.7
6	4.6	21.8	14.2	8.5
7	6.8	22.0	23.4	7.0
8	41.1	19.3	69.4	14.4
9	13.6	15.8	14.9	22.8
10	16.8	8.6	42.9	9.8
11	14.9	20.1	28.5	25.4
12	12.7	17.8	37.8	9.4
13	41.8	46.9	56.7	40.9
14	10.4	21.4	16.0	21.0
15	36.4	23.0	41.7	28.2
16	22.4	16.6	55.6	16.7
17	22.3	26.6	50.8	21.7
18	47.6	19.0	56.3	29.7
19	31.2	17.2	41.1	11.0
20	23.0	34.0	38.2	14.0
Mean	21.0	23.4	37.9	20.6
Standard deviation	±10.0	±7.4	±17.0	±9.3
Standard error of the difference between the two means				
	0.25		4.0	
Significance (P)				
	2.1		15,000:1	

* Recorded in counts/second/gm of tissue.

EXPERIMENT III

The Determination of Radioactive Iodine in the Granulomatous Lesions of Coccidioidomycosis and Sporotrichosis in Mice Receiving a Mixture of I-127 and I-131 Daily for a Period of Four Days

Part 1. Twenty mice were inoculated with *C. immitis* as described above and 20 matched mice were used as controls. Six days later a mixture of 5 mg of NaI and 10 μc of I-131 was injected subcutaneoussly into all mice. This was repeated daily for a total period of four days. The mice were sacrificed 8 hours after the last injection. A portion of the granulomas and livers in the infected animals and the greater omentums and the livers in the control mice were excised and their radioactivity determined as in Experiment I.

TABLE VIII

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with sporotrichosis and comparative tissues of control mice at 48 hours**

Mouse Number	Omentum		Liver	
	Control	Granuloma	Control	Infected
1	19.0	3.0	77.1	7.5
2	13.3	14.8	32.9	23.4
3	7.4	6.1	20.6	8.0
4	3.3	7.6	6.7	14.0
5	3.9	12.0	7.9	6.7
6	13.9	16.0	40.6	36.9
7	10.0	20.2	44.2	30.2
8	6.6	46.0	24.2	78.8
9	17.6	24.0	67.2	50.0
10	11.5	9.2	36.4	9.8
11	9.2	14.2	28.7	28.8
12	4.0	48.1	9.5	100.0
13	16.8	26.5	14.9	27.6
14	6.7	22.4	14.8	28.6
15	12.3	32.6	29.1	9.7
16	7.0	19.4	27.4	24.1
17	12.8	15.2	43.3	21.6
18	35.5	6.3	39.6	16.8
19	14.6	9.2	45.5	18.7
20	10.7	14.5	33.1	16.5
Mean	11.3	18.4	32.2	27.9
Standard deviation	±3.3	±12.0	±17.9	±17.6

Standard error of the difference between the two means		
	2.1	0.003
	Significance (P)	
	27:1	2:1

* Recorded in counts/second/gm of tissue.

Part 2. The experiment described in Part 1 of Experiment III was repeated employing *S. schenckii* as the infectious organism. The first injection of the mixture of I-127 and I-131 was administered on the twenty-seventh day after the inoculation of *S. schenckii.*

Results of Experiment III

Tables IX and X summarize the data obtained from Parts 1 and 2 of Experiment III. These indicate that there is no significant difference between the concentration of I-131 in the granulomas and omentums of mice with coccidioidomycosis and sporotrichosis. Similarly, there was no difference between the

TABLE IX

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with coccidioidomycosis and comparative tissues of control mice after receiving a mixture of I-127 and I-131 daily for four days**

Mouse Number	Omentum		Liver	
	Control	Infected	Control	Infected
1	132.4	129.3	153.1	196.7
2	27.7	53.7	38.5	39.9
3	112.0	97.1	132.9	122.3
4	165.2	196.0	185.4	122.3
5	89.1	133.8	62.7	104.0
6	138.7	175.0	168.2	158.9
7	213.2	132.2	176.4	142.8
8	259.9	107.6	228.0	114.9
9	173.6	8.2	218.6	8.9
10	250.5	92.7	304.5	81.3
11	179.7	316.7	161.6	241.6
12	77.1	110.0	100.9	83.6
13	100.0	537.2	79.3	288.3
14	118.3	99.3	131.7	97.4
15	60.0	101.4	57.8	93.8
16	282.1	214.5	327.3	223.1
17	150.9	87.0	177.9	64.7
18	121.1	189.5	101.2	135.6
19	152.2	56.1	197.9	61.3
20	199.2	107.7	287.0	73.3
Mean	150.2	147.2	164.5	123.5
Standard deviation	±65.5	±113.0	±79.2	±69.0
Standard error of the difference between the two means				
	0.003		0.5	
Significance (P)				
	2:1		2:1	

* Recorded in counts/second/gm of tissue. All mice were sacrificed 8 hours after the last injection.

TABLE X

*Radioactive iodine (I-131) uptake by the granulomatous tissues and the livers of mice with sporotrichosis and comparative tissues of control mice after receiving a mixture of I-127 and I-131 daily for four days**

Mouse Number	Omentum		Liver	
	Control	Infected	Control	Infected
1	195	278	224	199
2	611	1010	948	757
3	4380	2320	4970	1600
4	1570	2460	1970	1840
5	142	576	178	361
6	121	1590	93	1460
7	672	1410	734	912
8	77	296	63	232
9	698	871	1620	604
10	182	254	221	210
11	2450	1110	2480	1220
12	199	73	287	68
13	555	69	871	76
14	122	414	172	317
15	756	1120	824	334
16	1340	133	1460	168
17	818	206	825	291
18	711	1460	1460	811
19	256	73	962	49
20	221	486	235	430
Mean	804	810	1030	597
Standard deviation	±1004.3	±483	±1122	±597.4
Standard error of the difference between the two means	0.03		0.7	
Significance (P)	2:1		2:1	

* Recorded in counts/second/gm of tissue. All mice were sacrificed 8 hours after the last injection.

concentrations of I-131 in the livers of the mice with both infections when compared to controls.

DISCUSSION

Early investigative studies on the action of iodine in infectious diseases were devoted to the evaluation of the amount of iodine locally deposited in the disease process. Chemical analytical methods were used in these investigations for the determination of iodine and large amounts of iodine were necessarily administered to obtain data. It was generally agreed that granulomatous tissues con-

tained more iodine than normal tissues. Theories based on the above data proposed that the action of iodine was at a local level. The complex physiology of the general metabolism of iodine and also as it pertains to thyroid function was not considered in explaining the role of iodine in infections. The availability of radioactive iodine provided a new method for evaluating this problem.

Two different infectious organisms were used to note if any alteration in iodine metabolism was specifically characteristic of one disease process or was the result of a nonspecific reaction such as fever and malaise which may be associated with any disease. Sporotrichosis was employed because of the generally recognized specific therapeutic effect of iodine on the disease in man. It produces a mild prolonged infectious state in the mouse which results in moderate cachexia, but rarely death even over a period of three months. Unpublished data of ours indicates, however, that iodine exerts little or no therapeutic effect in sporotrichosis in the mouse. Coccidioidomycosis was chosen in contrast because it consistently produces a rapid fatal disease in approximately two weeks. In addition the specific granuloma of coccidioidomycosis has well-described histological differences from that of sporotrichosis.

In the first experiment it was noted that there was a decreased uptake of I-131 by the thyroids of mice with both diseases when compared to controls. This was true at 24 and 48 hours. As expected the infected mice lost varying amounts of weight. Therefore the I-131 uptake by the thyroids was calculated on the counts/gm. of animal as suggested by Meites and Wolterink (20). There was no correlation between the degree of cachexia as measured by weight loss and the depression of the ability of the thyroid gland to concentrate I-131.

The exact mechanisms by which these two generalized infections cause a decrease in the ability of the thyroid gland to concentrate I-131 is unknown. The theory that they act in a similar manner as non-infectious stress situations is attractive. Thus infections acting as stress would cause a shift in the activity of the anterior pituitary gland with increased secretion of adrenocorticotrophic hormone at the expense of the thryotrophic hormone. The role of the adrenal cortex in infections must be considered. Substances excreted by the adrenal cortex such as cortisone have been shown to decrease the thyroidal uptake of I-131. There is also the possibility that under the influence of infectious processes products other than thyroxin may be produced by the thyroid gland which would affect the normal metabolism of iodine.

Little is known about the effect of this apparent decrease in activity of thyroid function on the host parasite relationship in infectious diseases. One obvious purpose would be a regulatory sparing mechanism to compensate for the rise in metabolic activity which occurs in infections. Finally it should be pointed out that the amount of I-131 concentrated by the thyroid may not necessarily reflect all the complexities of thyroid function.

Our studies using minute doses of iodine as I-131 showed that there was a greater amount of I-131 in the granulomatous tissues than in the control tissues in both diseases. This was true at 12, 24, and 48 hours in coccidioidomycosis but only at 48 hours in sporotrichosis. The reasons for the difference in the two

diseases are speculative. They may be due to the fact that the mice with coccidioidomycosis were more acutely ill at the time of injection of I-131 or because of the characteristic differences in the local granulomas of the two diseases. We interpret our results to indicate that there is a definite concentration of iodine in the granuloma of coccidioidomycosis reaching a peak at 24 hours, and rapidly diminishing. The fact that the granuloma contains more iodine as early as 12 hours suggests that the iodine in part may be directly deposited in the granuloma.

The granuloma of sporotrichosis does not accumulate iodine to any greater extent than control tissue at 12 and 24 hours. At 48 hours, however, the granulomas did contain more I-131 than the omentum. This observation at 48 hours may indicate that the I-131 is deposited in excess in the granulomatous tissue; however this may represent a differential gradient of release of the iodine from the granulomatous tissue as compared to that of the omentum. Finally, it may be pointed out that the amount of iodine concentrated in the granulomatous tissue in both diseases represents a very minute fraction of the total administered dose of I-131 and that its concentrating ability is negligible when compared to that of the thyroid gland.

Sections of livers were taken from both infected animals and controls for evaluating the influence of infectious states on the iodine content of structures other than the local granulomatous processes and the thyroid gland. It was felt that the liver might reflect to a greater degree metabolic changes in iodine metabolism in infectious states, as it was recently pointed out (30) that the liver may act as an excretory organ for thyroxin. It was hoped that this additional data would aid in clarifying any observed alterations noted in the studies of the thyroid gland and granulomas.

The livers of the control animals were found to contain as much as or more iodine than that present in the omentum. The ratio between the livers and the omentums in all control animals was approximately 1:1 at 12 hours, 2:1 at 24 hours, and 3:1 at 48 hours.

The ratio between the livers and the granulomas in coccidioidomycosis was reversed when compared to those above. At 12 hours the ratio between the granulomas and the livers was approximately 2:1 and at 24 hours 3:1. At 48 hours the granulomas contained approximately twice as much I-131 as the livers of the infected animals. The data again reflects the concentration of I-131 which has occurred in the granulomatous tissues of coccidioidomycosis.

Differences are also observed in the amount of I-131 when the livers of the animals infected with coccidioidomycosis are compared to those of the controls. The infected livers at 12 and 24 hours contained approximately five times as much I-131 as the livers of the controls. However, at 48 hours the control livers contained approximately three times as much I-131 as the infected livers. We are unable to explain these observations. They point out the complexities of iodine metabolism and that the iodine metabolism of all organs studied—the thyroid gland, the granulomatous processes, and the livers—is altered in infections.

The relationship between the amount of iodine in the sporotrichotic granu-

lomas when compared to the liver of the same infected animals was different from that found in coccidioidomycosis. In coccidioidomycosis the granulomas contained more I-131 than the livers of the infected mice at all measured times. In sporotrichosis, however, the ratio between the livers and the granulomas was approximately 1:1 at 12 and 24 hours. At 48 hours the livers contained more than three times as much I-131 as was found in the granulomas. The control livers in sporotrichosis in direct contrast to coccidioidomycosis contained significantly more iodine than the infected livers at 12 and 24 hours. This was not true at 48 hours when the ratio between the two was approximately 1:1. The reason for these findings is not clear at the present time, but it is apparently not related to thyroid function as the thyroid gland of the mice with coccidioidomycosis and sporotrichosis reacted similarly.

Experiment III was performed in an effort to actually simulate therapeutic conditions in which a patient is given large daily doses of iodine. With the daily administration of I-127 and I-131 to mice with coccidioidomycosis and sporotrichosis it was hoped that any tendency of the granulomas to concentrate iodine might be accentuated with these larger doses. However, there was no difference in the amount of iodine in the various tissues of the mice with coccidioidomycosis and sporotrichosis and control tissues. We are therefore forced to conclude that iodine when given in therapeutic amounts no longer follows physiologic pathways of distribution in either the control or infected animals but instead completely saturates all tissues to approximately the same degree. Under such conditions even the granulomatous tissues of coccidioidomycosis display no concentrating ability. Our data does not represent the actual amounts of iodine in each organ, but does measure the comparative distribution of I-131 which occurred after the administration of I-127 and I-131 daily over the four-day period.

We cannot directly compare our data with that of previous investigators who used chemical analytical methods for the determination of the total amount of iodine in various organs. An additional deterrent to comparisons is the fact that the majority of previous studies on this subject were performed using animals infected with tuberculosis and syphilis and the metabolism of iodine in these diseases may differ from sporotrichosis and coccidioidomycosis. Finally it is obvious that more data must be obtained before the complex problem of the effect of iodine on infectious diseases is clarified.

CONCLUSIONS

1. The uptake of I-131 by the thyroid gland of mice infected with coccidioidomycosis and sporotrichosis was found to be significantly less in 24 hours and 48 hours than a similar group of control animals.

2. The uptake of I-131 at 12, 24, and 48 hours by the granulomatous tissues of mice with coccidioidomycosis was found to be significantly greater than by comparative control tissue.

3. The uptake of I-131 at 48 hours by the granulomatous tissues of mice with sporotrichosis was found to be significantly greater than comparative control tissue. This was not true at 12 and 24 hours.

4. There was marked alteration in the deposition of I-131 in the livers of the animals with both coccidioidomycosis and sporotrichosis when compared to the livers of the control mice.

5. Iodine was distributed evenly to the omentums, granulomatous tissues and the livers of the infected and control mice in both coccidioidomycosis and sporotrichosis when I-131 was administered daily over a 4-day period concomitantly with large doses of I-127.

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DISCUSSION

Dr. Juro Shintani (Long Beach, California): I should like to mention briefly the results of our investigation on this same subject which has been done at the Long Beach Veterans Administration Hospital and the University of Southern California. In the beginning we intended to study iodide distribution in experimental sporotrichosis by means of scintillation counters. However, we realized that the results of this technic would be of quantitative value and not qualitative. For example, even if one could demonstrate an increased uptake of iodine-131 in the sporotrichotic lesion, one still would not know whether this increased uptake was due to non-specific inflammatory edema or whether it actually represented an increased concentration of iodine-131 by certain cells in the granulomatous process.

It would be important to investigate the latter possibility because if such were the case, it would be a helpful clue in that it would localize the site of action of iodides at a specific cellular level. Therefore, instead of scintillation counters, it was decided to utilize a technic well suited for investigating this aspect, namely, radio-autography. Mice with localized sporotrichotic lesions were injected intraperitoneally with one millicurie of radio-active iodine (I-131) and then radio-autographs were made of the lesions. The results showed a diffuse distribution of iodine-131 in both infected and non-infected testes. No selective cellular localization was seen.

We also studied a clinical case of cutaneous North American blastomycosis. After giving him a tracer dose of iodine-131, we could demonstrate no selective uptake in the cutaneous lesion. His thyroid uptake was normal.

Dr. Theodore Cornbleet (Chicago, Ill.): I was glad to hear this paper because it gives us some background to a series of patients we treated for both local and systemic mycotic infections. We have been using iodides and thyroid

in a combined attack. Both are tolerated in what otherwise would be considered enormous doses. The results have been excellent. The last patient in our group was shown last month before the Chicago Dermatological Society. He had the systemic form of blastomycosis and was losing ground rapidly three and one-half months ago but is now about clinically cured. It is good to have an effective alternative treatment to that of the stilbenes, which as you know may be quite toxic.

DR. VICTOR D. NEWCOMER (in closing): I would like to thank the discussors of the paper and in view of Dr. Shintani's experience I would like to underscore one point: We have employed twenty-five microcuries of I-131 as a single dose in each of the mice. This dosage is approximately ten times the dose which is employed in tracer studies in man and perhaps might be the basis of why Dr. Shintani obtained negative results in evaluating the amount of I-131 deposited in granulomatous lesions in man.

I still cannot shed any light regarding the exact mechanism by which iodine affects the course of sporotrichosis and blastomycosis.

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