THE EFFECT OF LIGHT ON THE PHARMACOLOGICAL ACTION OF QUININE AND QUINIDINE SULPHATES.*†

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INTRODUCTION.

It is well known that solutions of quinine and quinidine sulphates exhibit a blue fluorescence. This fact suggested the idea that possibly the pharmacological and toxicological effects of these salts might be influenced by the action of light. Such an idea was not altogether far-fetched or too presumptive in view of some older observations by Tappeiner and Raab (1) who have found a difference in toxicity of solutions of the dye acridin for paramecia in light and darkness. And again in view of the difference in response of various isolated organs on treatment with eosin obtained by Amsler (2), Pick (3), and Kolm (4) under similar circumstances. Accordingly an experimental inquiry into the subject was undertaken.

In a previous communication one of the authors (5) has already called attention to the difference in toxicity in quinine and quinidine sulphate in frogs in light and darkness. It was shown that these salts when injected into frogs were much more toxic when the animals were subsequently exposed to light, the minimal lethal dose being much smaller in light than in darkness. Thus, for instance, a dose of 0.5 mgm. of quinidine sulphate per gram weight of frog, *Rana clamata*, injected into the anterior lymph sac on exposure to light produced paralysis of the frog in twenty-five minutes and complete arrest of the heart within thirty minutes. After injection, on the other hand, of another frog of the same species with an equivalent amount of the same drug with the animal placed in a dark cupboard, the dose was found to have been much less toxic, and the frog still alive twenty-four hours after the beginning of the experiment. It was further shown that the activation of quinine and quinidine sulphate was due chiefly to rays of shorter wave length belonging to the violet and ultraviolet regions of the spectrum and it was also established that the greater toxicity of the drugs in light was not due to the difference in temperature, inasmuch as even when the frogs were kept on ice and exposed similarly to direct sunlight the same effects were produced.

In the present communication the authors have undertaken to study the influence of light on small doses of the above salts on higher animals and more particularly albino rats. It has been found by Stübel (6) and others that ultraviolet rays of light penetrate to some extent below the surface of the body and it was thought possible that in this way the efficacy of quinine and quinidine solutions when injected into rats might be influenced by exposure to sunlight and other sources of ultraviolet radiation.

METHOD.

The method employed in the present work was the study of the behavior of trained albino rats in the circular maze and has been described repeatedly by Macht and collaborators in a number of papers (7),(8). The circular maze shown in

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Figure 1 is made with wooden base and aluminum walls. The base is 150 cm. in diameter and 4 cm. in thickness. Its upper surface is marked off by grooves into a series of concentric circles. The diameter of each of the circles is as follows, beginning with the outermost one: 140 cm., 120 cm., 100 cm., 80 cm., 60 cm., 40 cm., and 20 cm. Into the circular grooves are inserted sheets of aluminum 18.5 cm. high and 0.8 mm. thick. Each strip of aluminum is cut just 10 cm. shorter than the length of the circular grooves into which it is to be fitted, thus giving an opening into the alley. By means of this arrangement it is possible to slide the aluminum around in its groove and thus to place the entrance in any desirable position. In the present investigation, the openings or entrances to the alleys were placed in the position indicated in Figure 1, there being 7 openings so arranged that the rat had to make alternate turns to right and left, in the order indicated by Nos. 1 and 7. In addition to the doors or openings, the alleys are provided also with obstructing partitions, which form a number of blind-cul-de-sacs. A wire screen prevents the animals from crawling over the top.

The study of the behavior of the rats in the circular maze is begun by placing an animal in the center of the maze and feeding it from the bowl *F* for three successive days. During these three preliminary feedings, which last from ten to fifteen minutes, the entrance *7* is blocked off, so that the animal may not roam around. On the fourth day, the rat is placed in the cage *E*, then the trap-door *T* is raised and the animal allowed to enter the first alley. The animal then gradually learns to find its way to the center of the maze, when it is taken out and the experiment is repeated. Generally three trials are made on each day. For work with the maze, albino rats, which are very tame, must be employed. The animals must be handled gently with the hands and under no circumstances must they be picked up with forceps or similar instruments. The most suitable animals are found to be rats approximately sixty to ninety days old. Older animals are apt to be sluggish, while very young rats do not learn the maze problem so readily. Ordinarily, the albino rats learn the maze problem in about two weeks, and sometimes within a shorter period of time. An animal is considered to have solved the maze problem when it has learned to find its way into the center of the maze by the shortest route, that is, without any errors, on three successive trials. The technic of trials is described more in detail by Hubbert (9).

ANALYSIS OF THE DATA FURNISHED BY THE MAZE.

The maze problem enables the psychologist to study the mode of learning of a rat. In studying the effect of drugs, the maze problem can be utilized in two ways. Animals may be subjected to the influence of drug action first and then trained in the maze with the purpose of ascertaining the effect on the rate of learning. Again, animals may be first taught to solve the maze problem and then the effect of a drug is studied in reference to its influence on their behavior, memory-habit, etc. Furthermore, other data can be obtained from the maze, after administering drugs to rats, which may show the effect on neuromuscular coördination, and various somatic changes. As to exactly what the mechanism of learning the maze problem may be, the explanations given by various psychologists differ widely. Among the hypotheses which have been advanced to account for the reintegration of conduction paths in learning, there are at least three which stand out as rather op-

posed to one another in respect to the neural processes which they imply (10). The hypothesis suggested by Ladd and Woodworth (11) assumes inhibition of successive activities as the fundamental process which results in the selection and fixation of random activities. The second hypothesis, given by Angell and others (12), assumes nervous reinforcement as the fundamental process by which successive acts become linked together in habit-formation. The third hypothesis (Watson (13)) depends chiefly upon the chance spreading of nervous excitation, or the simultaneous activation of two afferent pathways in such a way that the final common part of one is able to divert the discharge of the other and so bring about a permanent connection between itself and this afferent path. These hypotheses by no means exhaust the theoretical considerations of the maze problem (Dashiell (14)).

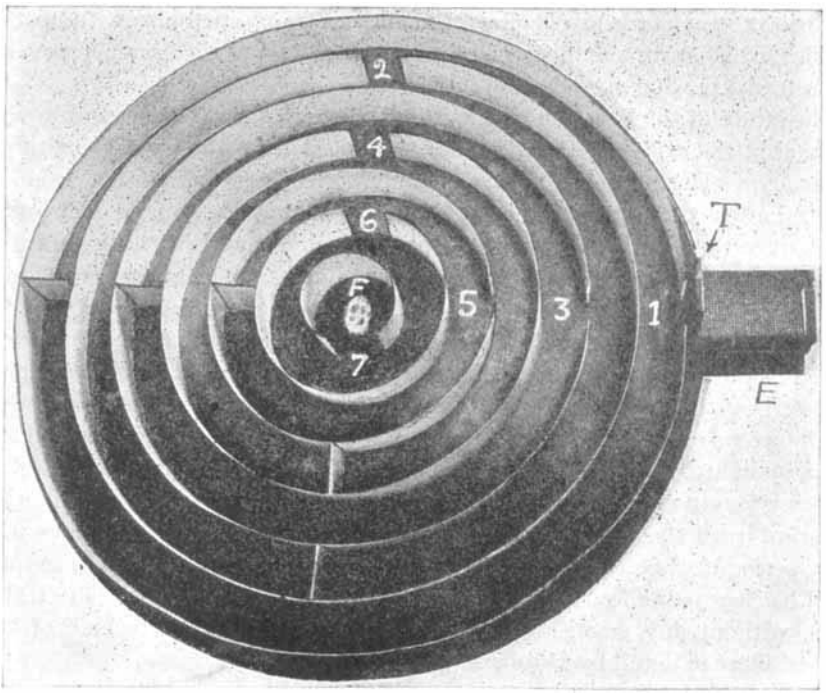

Fig. 1. Circular Maze Viewed from Above.
E, entrance cage; *T*, trap door leading into first alley; Nos. 1 to 7 indicate the gates to the successive alleys; *F*, food.

For the study of the drug action, however, the various theoretical considerations are of secondary importance and the data obtained are of a much more definite nature, as will be seen from the following exposition.

THE EFFECT OF SUNLIGHT AND ULTRAVIOLET RAYS ON THE BEHAVIOR OF NORMAL RATS.

Six young adult male rats aged about six months and 3 old male rats aged about twelve months were employed for the control experiments. The animals were carefully trained in the circular maze and the effects of exposure to light were studied on their behavior. At first the animals were exposed to direct sunlight;

this was found to have practically no effect on their behavior. Subsequent to exposure to the sun a series of experiments were made with exposure of the animals to the radiation of a mercury vapor quartz lamp (Hanovia Alpine Sun Lamp*) for periods varying from ten to fifteen minutes at a time and the behavior of the animals was again observed.

The results obtained were quite definite and are expressed in Tables 1 and 2.

TABLE 1.

Effect of exposure to ultraviolet rays (Alpine Sun Lamp) on behavior of rats in the circular maze. A. Young rats.

DATE AND LENGTH OF EXPOSURE	NUMBER OF EXPERIMENT	TIME					ERRORS				
		Before	Average	After	Average		Before	Average	After	Average	
12-11-22 15 min.	1	14 8 8	10	9 5 7	7		1 0 0	0.3	0 0 0	0	
	2	12 7 5	8	8 5 7	6.7		1 0 0	0.3	0 0 0	0	
	3	6 16 5	9	10 5 5	6.7		0 1 0	0.3	1 0 0	0.3	
	4	9 16 13	12.7	6 5 5	5.3		0 1 1	0.7	0 0 0	0	
	5	13 9 8	10	8 7 8	7.7		1 0 0	0.3	0 0 0	0	
	6	6 6 6	6	6 5 5	5.3		0 0 0	0	0 0 0	0	
			9.3		6.4			0.33		0.05	
1-20-23 10 min.	7	28 22 9	19.7	21 9 7	12.3		0 1 0	0.3	2 0 0	0.7	
	8	30 7 12	16.3	22 7 20	16.7		2 0 0	0.7	2 0 1	1.0	
	9	36 23 14	22.3	15 11 8	11.3		1 0 0	0.3	0 0 0	0	
	10	23 60 10	31	15 9 9	11		0 3 0	1.0	0 0 0	0	
	11	27 7 28	20.7	6 12 5	7.7		1 0 3	1.3	0 1 0	0.3	
	12	8 10 9	9	8 7 8	7.7		0 0 0	0	0 0 0	0	
			19.8		11.1			0.60		0.33	
1-30-23 15 min.	13	10 7 15	10.7	7 7 7	7		0 0 0	0	0 0 0	0	
	14	12 20 12	14.7	11 6 10	9		0 1 1	0.7	1 0 1	0.7	
	15	18 9 14	13.7	31 26 9	22.7		1 0 0	0.3	* 2 0	?	
	16	10 15 12	12.3	7 9 6	7.3		1 0 0	0.3	0 0 0	0	
	17	12 13 11	12	8 8 5	7		0 1 0	0.3	0 1 0	0.3	
	18	9 6 5	6.7	6 11 18	11.7		0 0 0	0	0 1 3	1.3	
			11.7		11.8			0.27		0.467	
			(11.3)		(8.4)			(0.26)		(0.48)	
2-6-23 15 min.	19	13 7 7	9	9 6 6	7		0 0 0	0	0 0 0	0	
	20	17 7 12	12	30 6 6	14		0 0 1	0.3	3 0 0	1.0	
	21	96 14 15	41.7	30 17 8	18.3		3 1 0	1.3	2 0 0	0.7	
	22	21 8 8	12.3	12 7 6	8.3		0 0 0	0	0 0 0	0	
	23	9 8 28	15	9 9 17	11.7		0 0 1	0.3	0 0 2	0.7	
	24	17 7 7	10.3	8 7 7	7.3		0 0 0	0	0 0 0	0	
			16.7		11.1			0.32		0.40	
2-8-23 15 min.	25	10 5 6	7	5 6 6	5.7		0 0 0	0	0 0 0	0	
	26	8 5 5	6	9 6 7	7.3		0 0 0	0	0 0 0	0	
	27	30 6 7	14.3	13 10 9	10.7		0 0 0	0	0 0 0	0	
	28	21 13 15	16.7	7 7 8	7.3		2 0 2	1.3	0 0 0	0	
	29	13 32 9	18	10 8 8	8.7		0 3 0	1.0	1 0 0	0.3	
	30	5 8 29	14	6 7 6	6.3		0 0 3	1.0	0 0 0	0	
			12.7		7.7			0.55		0.05	

* = many errors.

TABLE 2.

Effect of exposure to ultraviolet rays (Alpine Sun Lamp) on behavior of rats in the circular maze. C-1. Old rats.

DATE AND LENGTH OF EXPOSURE	NUMBER OF EXPERIMENT	TIME					ERRORS				
		Before	Average	After	Average		Before	Average	After	Average	
7-22 10 min.	1	6 6 6	6	6 6 7	6.3		0 0 0	0	0 0 0	0	
	2	7 6 5	6	5 6 5	5.3		0 0 0	0	0 0 0	0	
	3	7 7 8	7.3	8 5 5	7		0 0 0	0	0 0 1	0.3	
			6.4		6.2			0		0.10	
12-14-22 15 min.	4	15 12 6	11	10 7 9	8.7		1 1 0	0.7	1 0 0	0.3	
	5	7 8 6	6.3	7 7 9	7.7		0 0 0	0	0 1 1	0.7	
	6	7 6 8	7	6 6 6	6		0 0 0	0	0 0 0	0	
			8.1		7.5			0.23		0.33	
1-20-23 15 min.	7	24 10 10	14.7	12 25 12	16.3		0 0 0	0	0 1 0	0.3	
	8	6 8 6	6	11 5 6	7.3		0 0 0	0	1 0 0	0.3	
	9	21 6 7	11.3	10 7 7	8		1 0 0	0.3	0 0 0	0	
			10.7		10.6			0.10		0.20	
1-23-23 15 min.	10	8 8 8	8	10 8 12	10		0 0 0	0	0 0 0	0	
	11	7 6 6	6.3	26 9 7	14		0 0 0	0	2 1 0	1.0	
	12	10 7 15	10.7	31 7 8	15.3		0 0 0	0	2 0 0	0.7	
			8.3		13.1			0		0.57	
1-30-23 15 min.	13	13 33 33	29.7	21 11 17	16.3		1 3 1	1.7	1 0 0	0.3	
	14	28 27 11	22	7 8 7	7.3		1 2 0	1.0	0 0 0	0	
	15	9 18 7	11.3	8 9 21	12.7		0 1 0	0.3	0 0 2	0.7	
			21.0		13.1			1.00		0.33	
2-3-23 15 min.	16	28 9 9	15.3	24 31 27	27		1 0 0	0.3	0 0 0	0	
	17	12 7 7	8.7	6 6 6	6		0 0 0	0	0 0 0	0	
	18	34 17 11	20.7	20 9 22	17		1 1 1	1.0	0 0 1	0.3	
			14.9		16.7			0.43		0.10	
2-6-23 18 min.	19	17 9 31	19	11 53 14	26		1 0 3	1.3	0 3 0	1.0	
	20	7 7 33	15.7	12 7 6	8.3		0 0 3	1.0	2 0 0	0.7	
	21	12 17 29	19.3	21 10 23	18		0 1 3	1.3	1 0 1	0.7	
			18.0		14.1			1.20		0.80	
2-8-23 15 min.	22	7 14 14	11.7	11 13 16	13.3		0 0 0	0	0 0 0	0	
	23	8 10 7	8.3	7 5 5	5.7		0 0 0	0	0 0 0	0	
	24	15 16 15	15	8 13 15	12		1 0 1	0.7	0 2 0	0.7	
			11.7		10.3			0.23		0.23	

A careful analysis of all the data contained in the above tables as well as other observations on the rats before and after radiation indicate that the effect of ultraviolet rays on the behavior of rats in the maze is either negative or more often slightly stimulating. This stimulating effect on the muscular activity of the animals is of a temporary character, persisting only for a few hours. The animals were always found to have gotten back to normal within twenty-four hours. The more intimate explanation of the results obtained is not quite clear. It is possible that increased muscular activity is merely a result of an irritating action by the rays. On the other hand no other deleterious effects produced by these rays were

* Loaned by courtesy of the Hanovia Chemical & Mfg. Co., Newark, N. J.

noted. Even conjunctivitis occurred only occasionally and was never very marked. The general condition of the animals, their nutrition and other behavior were not found to be impaired in any way.

EFFECT OF LIGHT ON INJECTIONS OF DRUGS.

Having ascertained the influence exerted by light itself on the animals experiments were begun in order to determine the relation of light and darkness to the potency of the fluorescent solutions of quinine and quinidine sulphate. The procedure employed was to first determine the running time and number of errors, if any, of a given rat on three successive trials and then to inject a solution of one of the drugs and expose the animal either to light or to darkness and study its behavior after a given period of time (fifteen to thirty minutes after injection). Inasmuch as solutions of sodium chloride reduce the fluorescence of quinine and quinidine sulphates to some extent the drugs were injected as a rule in aqueous solution. Injections were made in some experiments intraperitoneally and in others subcutaneously. It was found that both intraperitoneal and subcutaneous injections produced exactly similar effects except that drugs introduced by the intraperitoneal route were absorbed a little more rapidly.

TABLE 3.
Effect of quinine sulphate in light.

EXPERIMENT	SERIES OF RATS	DOSE	EXPOSURE	BEFORE TREATMENT		AFTER TREATMENT	
				Average speed	Number of errors	Average speed	Number of errors
		mgm.	minutes	seconds		seconds	
1. Sunlight	A	2	10	9.0	0	9.0	1
2. Sunlight	A	2	10	6.3	0	14.3	4
3. Sunlight	A	2	10	5.6	0	26.3	4
4. Sunlight	C	4	10	6.0	0	7.6	0
5. Sunlight	C	4	10	5.3	0	5.3	0
6. Sunlight	A	6	20	7.7	0	Stalled and muscular weakness	
7. Sunlight	A	6	20	5.0	0	Stalled and muscular weakness	
8. Sunlight	A	6	20	5.0	0	Stalled and muscular weakness	
9. Sunlight	C	8	15	5.7	0	80.0	10
10. Sunlight	C	10	15	10.0	2	Ataxia. Does not run	
11. Diffuse sunlight	A	6	15	14.0	1	Stalled	
12. Diffuse sunlight	A	6	15	7.0	1	Stalled	
13. Diffuse sunlight	A	6	15	11.7	1	62.0	2
14. Quarts lamp	C	6	15	5.7	0	9.3	1
15. Quarts lamp	A	4	15	22.0	4	23.0	0
16. Quarts lamp	A	4	15	20.0	6	44.0	6
17. Quarts lamp	A	8	15	15.3	2	Stalled. Muscular weakness	
18. Quarts lamp	C	8	20	15.7	2	Stalled. Very toxic	
19. Quarts lamp	A	6	20	11.3	2	30.0	2. weakness
20. Quarts lamp	A	6	20	33.0	4	Completely lost	
21. Quarts lamp	C	8	10	16.0	4	Does not run	
22. Quarts lamp	C	8	10	8.0	0	200.0	Very many
23. Quarts lamp	A	2	15	35.0	6	29.0	4
24. Quarts lamp	A	2	25	22.0	6	12.3	0
25. Quarts lamp	A	2	25	8.7	0	19.7	4

TABLE 4.
Effect of quinine sulphate in dark.

EXPERIMENT	SERIES OF RATS	DOSE	DURATION	BEFORE TREATMENT		AFTER TREATMENT	
				Average speed	Number of errors	Average speed	Number of errors
		mgm.	minutes	seconds		seconds	
1. In dark	A	6	25	13.0	2	Stalled but more active than in light	
2. In dark	A	6	20	6.0	0	43.0	4
3. In dark	A	6	20	5.7	0	Stalled but more active than in light	
4. In dark	C	8	30	12.7	2	63.3	3
5. In dark	C	10	15	9.0	0	Stalled and ataxic	
6. In dark	A	6	15	7.0	0	102.5	2
7. In dark	A	6	15	24.3	3	Does not run	
8. In dark	A	6	20	9.7	0	85.0	3
9. In dark	C	4	20	9.0	0	15.0	2
10. In dark	A	4	20	13.0	0	27.3	1
11. In dark	A	8	15	12.7	0	300.6	3
12. In dark	C	8	18	7.0	0	Lost but more active than in light	
13. In dark	A	6	20	6.3	0	100.0	2
14. In dark	A	6	20	16.7	3	100.5	2
15. In dark	C	4	25	14.7	4	27.0	2
16. In dark	A	2	22	8.7	2	7.7	0
17. In dark	A	2	24	8.7	0	9.3	0
18. In dark	A	2	20	18.0	4	12.7	2
19. In dark	C	6	15	10.0	0.	20.0	2
20. In dark	C	6	18	6.0	0	9.0	0
21. In dark	A	4	28	9.3	0	8.7	0
22. In dark	A	4	30	11.7	0	13.3	0
23. In dark	A	3	20	6.8	0	7.0	0
24. In dark	A	3	30	7.0	0	7.0	0
25. In dark	A	4	20	12.3	0	11.0	0
26. In dark	A	4	20	12.0	1	12.0	1

The effect of the injections of quinine and quinidine were studied on the same rats both in the dark and on exposure to light so that the difference, if any, could be more easily detected. In order to study the effect of non-exposure to light the animals were kept in a cage covered by a dark blanket allowing, however, perfect ventilation. The effects of light waves were studied in three ways; some animals were kept in diffused daylight after injection, others were exposed to direct sunlight, and still others were exposed to the ultraviolet radiation of a quartz lamp (Hanovia Alpine Sun Lamp). It is needless to state that care was taken to radiate the

animals in coarse meshed wire cages without the intervention of glass windows which cut out a large proportion of short waves. The results obtained are tabulated in Tables 3 to 6.

In the tables the average running time of the rats and the number of errors committed before and after injection of the drugs are indicated. In addition to the data expressed in the tables observations were made on the general behavior, muscular activity, etc., of the animals which are referred to in the general discussion. Two series of rats were studied: Series A comprised 12 young adult rats, the average weight of which was about 125 grams, Series C comprised older rats of a larger size, the average weight of each being 250 grams. These facts should be borne in mind on studying the tables. The doses indicated are the total injected in each animal; in other words they indicate the number of milligrams per 125 grams weight of rats in Series A and 250 grams of rat in Series C.

TABLE 5.
Effect of quinidine sulphate in light.

EXPERIMENT	SERIES OF RATS	DOSE	EXPOSURE	BEFORE TREATMENT		AFTER TREATMENT	
				Average speed	Number of errors	Average speed	Number of errors
		mgm.	minutes	seconds		seconds	
1. Sunlight	A	2	10	7 3	0	Very bad. lost way	Completely
2. Sunlight	A	2	10	9 3	0	8 6	1
3. Sunlight	A	2	10	11.3	0	9 7	0
4. Sunlight	C	4	10	5 6	0	10.3	1
5. Sunlight	A	6	20	7 6	1	Stalled. weakness	Muscular
6. Sunlight	A	6	20	10.0	1	Stalled. weakness	Muscular
7. Sunlight	A	6	20	5.7	0	Stalled. weakness	Muscular
8. Sunlight	C	8	15	6 3	0	19 0	2
9. Sunlight	C	8	15	5.0	0	20.0	2
10. Sunlight	C	10	15	7 0	1	Ataxia.	Stalled
11. Sunlight	C	10	15	5 7		Ataxia.	Stalled
12. Diffuse sunlight	A	6	16	15 0	1	Stalled	
13. Diffuse sunlight	A	6	15	14 3	1	Stalled	
14. Diffuse sunlight	A	6	16	10 3	2	Stalled	
15. Quarts lamp	C	6	15	7 7	0	9 3	6
16. Quarts lamp	A	4	15	23 3	4	57.0	4
17. Quarts lamp	A	8	15	31 0	5	150.0	6
18. Quarts lamp	C	8	20	23 6	3	Stalled.	Very toxic
19. Quarts lamp	A	6	20	12 3	2	210 0	10
20. Quarts lamp	A	6	20	17 0	6	22.7	4
21. Quarts lamp	A	6	20	8 7	0	40 0	2

TABLE 6.
Effect of quinidine sulphate in dark.

EXPERIMENT	SERIES OF RATS	DOSE	DURATION	BEFORE TREATMENT		AFTER TREATMENT	
				Average speed	Number of errors	Average speed	Number of errors
		mgm.	minutes	seconds		seconds	
1. In dark	A	6	30	8.0	0	Stalled	
2. In dark	A	6	30	7.3	0	Lost but more active than in light	
3. In dark	A	6	25	8.7	0	Stalled	
4. In dark	C	8	35	14.3	3	22.0	1
5. In dark	C	8	25	9 0	0	11.0	0
6. In dark	C	10	15	15 0	2	58.0	1
7. In dark	C	10	17	17 3	3	Stalled but less depressed than in light	
8. In dark	A	6	26	10 0	0	33.0	1
9. In dark	A	6	24	13 0	1	Stalled but more lively than in light	
10. In dark	A	6	22	7.7	0	Stalled but more lively than in light	
11. In dark	C	8	20	25.3	4	61.0	2
12. In dark	C	8	28	6.3	0	80.0	2
13. In dark	A	4	15	14.0	2	11.0	0
14. In dark	A	8	25	26.0	4	41.6	0
15. In dark	A	6	15	11.0	2	65.0	2
16. In dark	A	6	20	16.7	4	Does not run	
17. In dark	A	6	25	23.6	2	29.3	2
18. In dark	C	4	23	7.3	0	10.7	2
19. In dark	C	4	25	9.7	0	24.7	2
20. In dark	A	2	28	18.3	2	14.0	2
21. In dark	A	2	26	7.0	0	5.0	0
22. In dark	C	6	20	20.7	2	19.3	0
23. In dark	A	4	20	17.7	4	28.0	4
24. In dark	A	4	23	10.0	0	11.0	0
25. In dark	A	4	25	15.3	2	15.0	2
26. In dark	C	8	10	31.0	4	18.3	4
27. In dark	A	2	20	38.3	0	16.3	0
28. In dark	A	2	17	26.0	2	17.0	2
29. In dark	C	4	20	7.7	0	12.0	2
30. In dark	C	4	20	20.3	5	41.7	5

RESULTS.

An analysis of all the data obtained with injections of quinine and quinidine sulphates in the white rats brought out pretty definitely a number of facts. It was found that when the animals were exposed to light the action of the drugs was intensified. This was especially true when smaller doses of the alkaloids were injected. Thus, for instance, in the case of quinine sulphate when doses varying from 2 to 4 mgm. of the salt were injected into the rats of series A, the effect in darkness after exposure, for fifteen minutes, was very slight indeed. The running time was slightly increased, the average speed being about 20 per cent. slower than normal. On the other hand when the same rats were injected with the same doses of quinine sulphate and the animals were exposed to light, the running time was in-

creased about 100 per cent. Again a number of the younger rats injected with 6 mgm. of quinine sulphate and kept in the dark showed practically no change in the running speed but made more mistakes than before injection (increase from 3 errors before injection to 10 after injection). These same rats injected with the same doses of quinine sulphate (6 mgm.) and exposed to light were "stalled," an expression used to indicate that the animals were completely lost in the maze, could not find their bearings, made innumerable mistakes and never reached the center. In the case of the larger rats an injection of 4 mgm. of quinine produced no change either in the running speed or the number of mistakes made by the rats when the animals were kept in the dark after injection. On the other hand the same animals injected with the same dose of the drug and exposed to light were 50 per cent. slower in their running time and showed a marked increase in the number of mistakes made.

The effects of quinidine were equally or perhaps even more striking than those with quinine. Thus, for instance, it was found that when the small rats, Series A, were injected with doses from 2 to 4 mgm. and were kept in the dark for fifteen minutes no change whatever was produced in the running time or the number of mistakes made by the animals. On the other hand the same doses of quinidine sulphate on exposure of the animals to light caused a slowing of about 140 per cent. in the running time and also an increase in the number of errors. A number of experiments made with doses of 6 mgm. in rats of Series A were even more striking. These animals when kept in the dark showed a slowing in the speed of about 120 per cent. as compared with the normal running time whereas the same animals injected with the same doses of the drug and exposed to light showed an increase in speed of 621 per cent. The difference between the sunlight and radiations of the quartz lamp were not very marked although the ultraviolet radiations of the lamp produced somewhat greater potentiation of the drug action. A comparative study of quinine and quinidine on the rats both in the dark and in light revealed another interesting feature. As a result of the analysis of all the data it was found that quinine was distinctly more toxic than its optic isomere, quinidine. This was evident after injections of both small or therapeutic doses and large or lethal doses of the drugs. The effect of smaller doses may be noted in the tables. Extremely toxic or lethal doses showed a similar difference in toxicity between the laevo-gyrous quinine and the dextro-gyrous quinidine, as may be illustrated by the following experiments.

Experiment A. June 8, 1922. Rat weighing 100 grams was injected intraperitonally with 20 mgm. of quinidine sulphate in 0.5 solutions and the animal was placed in a wire cage and exposed to direct sunlight. Five minutes after injection the animal's breathing became shallow and the rat appeared to be very sick. Ten minutes after injection convulsions appeared. Twenty minutes after injection the animal was in deep coma and thirty-five minutes after injection the animal was dead.

Experiment B. Rat weighing 100 grams, injected intraperitionally with 20 mgm. of quinidine sulphate in 0.5 solution and placed in a dark cupboard. Forty minutes after injection the animal is still alive and running about. One hundred and ten minutes after injection the animal is depressed but sitting up and not very sick. The animal was left in the dark cupboard and on the following day was alive and apparently recovered.

Exactly similar experiments were made on rats with solutions of quinine sulphate and a similar difference in toxicity on exposure to light and darkness, re-

spectively, was noted. The lethal dose of quinine sulphate, however, was smaller than that of quinidine. As a result of numerous experiments concerning the lethal dose of the two alkaloids on rats it was found that 20 mgm. of quinidine sulphate per 100 grams weight of rat were fatal to the animal within one hour of the time of injection. In the case of quinine, 15 mgm. of the sulphate per 100 grams of rat were sufficient to produce the same results.

DISCUSSION.

A careful study of all the data obtained, both those expressed in the tables together with notes on the general behavior of the animals, reveals clearly that light plays an important rôle in relation to the pharmacological activity of solutions of quinine and quinidine sulphates for rats. Injections of these drugs were followed by depression and toxic signs much more rapidly and after smaller doses when the animals were exposed to sunlight or quartz lamp rays than when they were kept in the dark. Such waves of light penetrate sufficiently far through the surface of the body to produce an activation of the drugs present in the circulating blood. Such a result is not altogether surprising inasmuch as it has been found by Stübel and other investigators (15) that ultraviolet waves of light do penetrate through various tissues to a greater or less extent. The results obtained with quinine and quinidine in the present study are even more convincing in view of the fact that a previous investigation concerning the effects of sunlight and ultraviolet light on the behavior of normal rats indicated that if anything, such a radiation is followed by a stimulation and not a depression as indicated by the behavior of the animals in the maze. The difference in toxicity as between light and darkness of the two alkaloidal salts studied was noted both after small or what may be called therapeutic doses of the drugs as well as after extremely large or lethal doses of the same.

It is also of interest to note the difference in the relative toxicity of quinine and quinidine, which are chemically isomeric and differ only in respect to the configuration of molecules, quinine being laevo-gyrous while quinidine is dextro-gyrous. Here as in the case of other optic isomers it is interesting to find that the laevo-gyrous variety is the more toxic one. This difference in the toxicity between quinine and quinidine for animals applies also to the relative toxicity for plant protoplasm as has been pointed out by one of the authors elsewhere (16). The influence of light on the activity of quinine and quinidine as noted by the authors for frogs and rats applies also in a measure to their pharmacological action on isolated organs. Experiments are in progress with a view to ascertain the effects of light on the action of quinine and quinidine on the isolated heart and the results so far obtained already warrant the statement that both quinine and quinidine on exposure to light radiation produce more rapid and more poisonous effect on the action of the heart. In view of the recent introduction of quinidine into the therapy of certain heart conditions these findings ought to be borne in mind. It is not too much to assume that exposure of white patients to direct sunlight and possibly to ultraviolet radiation may intensify the therapeutic effects of small doses of quinidine.

SUMMARY.

The effect of light on the behavior of normal rats and of rats injected with solutions of quinine and quinidine sulphates was studied in respect to their behavior in the circular maze. It was found that:

1. Sunlight and ultraviolet radiations from a quartz lamp produce either no effect or a stimulating effect on normal rats.

2. The pharmacological activity of quinine and quinidine sulphates was greater in animals exposed to light than those kept in darkness.

3. The absolute lethal doses of quinine and quinidine were smaller for animals kept in light than those kept in darkness.

4. As between the two optic isomers quinine and quinidine, the laevo-gyrous variety (quinine) was more toxic than the dextro-gyrous variety (quinidine).

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SUPRARENIN (SYNTHETIC EPINEPHRIN).*

BY CASIMIR FUNK, HARRY E. DUBIN AND LOUIS FREEDMAN.

One of the most notable achievements of modern chemistry and science is the synthesis of the naturally occurring alkaloid, epinephrin. This drug, which is probably the most powerful physiologic substance known, is found in the medulla of the suprarenal gland in all animals and was first obtained in an impure condition in 1897 by Abel and Crawford. It was finally purified by Takamine in 1901, and its chemical structure was definitely established in 1903. From then on, efforts were directed toward its synthesis in the laboratory, this being accomplished independently by several workers a year later.

The synthesis of this highly important pharmaceutical was not considered complete, however, until the racemic form, in which it is obtained when synthesized, was resolved into its two optically active components. This was accomplished several years later by Stolz and his co-workers by means of fractional crystallization of the bitartrates, and also by the action of a fungus—*penicillium glaucum.*

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