The influence of kairin, thallin, hydrochinon, resorcin, and antipyrin, on the heart and bloodvessels / by H.G. Beyer.

Extracted from the
American Journal of the Medical Sciences for April, 1886.

THE

INFLUENCE OF KAIRIN, THALLIN, HYDROCHINON, RESORCIN, AND ANTIPYRIN,

ON THE

HEART AND BLOODVESSELS.

BY

H. G. BEYER, M.D., M.R.C.S.,

PASSED ASSISTANT SURGEON, U. S. N.;
HONORARY CURATOR, SECTION MATERIA MEDICA, U. S. NATIONAL MUSEUM.

Chemists, for a number of years, have been industriously experimenting, hoping to find a way to produce quinine artificially. The result has been the discovery of a number of substances, some of them belonging to the phenol series of organic compounds, and possessing to an eminent degree the power of reducing hyperpyrexial temperatures.

The literature on these newly discovered antipyretics has already been enriched by a very large number of contributions, and the *Index Medicus* for 1884 and 1885 contains about ninety-four references, of which forty-two are on antipyrin, thirty-four on kairin, nine on resorcin, seven on thallin, and but two on hydrochinon. Most all of these very valuable contributions, however, treat of these remedies as antipyretics only, and of their power of reducing the temperature in fever, while very few, indeed, are devoted to their physiological action. The busy practitioner is too often obliged to remain satisfied with this, having no time to investigate for himself.

No detailed series of experiments on the influence of these remedies upon the circulatory apparatus has, so far, been published, and yet their relation to that apparatus seems all-important, for no intelligent idea of their manner of action can possibly be formed until more is

known about this; nor can the discrepancies in the results, so far as they have been recorded in the different cases, be satisfactorily explained.

It is through the agency of the bloodvessels, and the blood which circulates within them, that not only the temperature of the various organs of the body is constantly being equalized, but also that the superabundant heat, dangerous to the economy, is thrown off. As is well known, the constant or normal temperature peculiar to animals depends upon the maintenance of a proper balance between the amount of heat generated within the organism, and the amount given off to the surrounding medium through the agency of the bloodvessels of the skin, the lungs, etc.

Thus, when heat production is feeble and the temperature of the surrounding medium low, the cutaneous vessels will be found contracted, and the amount of blood which flows through them in a unit of time will, consequently, be relatively small. On the other hand, these vessels will be found dilated, and an abundant flow of blood take place through them, when heat production is increased and the temperature of the surrounding medium is high. Hence, it is evident that any interference with this important function of the circulatory apparatus must, necessarily, greatly influence the temperature of the body, and anything tending to lower the tone of the bloodvessels, or weaken the heart's action, at once deprives the organism of its most effective means for heat regulation. In the condition known as fever, the temperature peculiar to the animal, or its normal temperature, exists no longer, and in place of it we find a higher one.

It is neither possible nor, perhaps, desirable to enter here into the different theories of heat production, nor into a discussion of the gradual evolution of our present theory of the causation of fever, deeply interesting and instructive though they be from a pathological point of view; it is sufficient for our purpose to know the generally admitted fact that any abnormal increase in the temperature of the body can only be due either to an increased heat production or to a decrease in heat radiation, or to both these combined.

Kairin, thallin, hydrochinon, resorcin, and antipyrin, have all been found to reduce abnormal temperatures to a greater or less degree, in almost all febrile disorders promptly though perhaps not permanently. An experimental inquiry into the probable relations of these new antipyretics to the circulatory apparatus seemed, therefore, very desirable, and the results obtained in the following experiments will, it is hoped, quite sufficiently justify the attempt to solve the problem.

In order to work out the details of their influence on the several parts of the circulatory apparatus, we are naturally obliged to turn our attention to the cold-blooded animals. The animals used for experi-

mentation in this inquiry were the bull-frog, or *Rana pipieus*, Linn., the marsh-frog, or *Rana pallustris*, Leconte, and the slider-terrapin, or *Pseudemys rugosa*, Shaw.

For convenience of description, the experiments have been arranged into two groups.

I. Experiments on the work done by the heart when isolated from the central nervous system.

II. Experiments on the bloodvessels: (1) on the flow through the vessels of animals the brains and spinal cords of which had been destroyed; (2) on the lingual vessels of curarized frogs.

In addition to this, a short account of the influence of these drugs upon the corpuscular elements of the blood and the coagulation of blood will be given.

A detailed description of the method and apparatus used in these experiments having already been given in the number of this journal for July, 1885, a short *résumé* will here suffice for an intelligent understanding of how the results were obtained.

In the case of an experiment on the heart, this organ was isolated and left *in situ*. Canulas were then introduced into at least two of the great venous trunks leading directly into the sinus (only one in the frog), and tied as far as possible from the latter so as to keep them as well as the heart under constant and easy observation.

Two canulas were likewise introduced and tied into two of the arterial trunks coming from the ventricle. The venous or inflow canulas were connected with Mariotte's flasks containing the different feeding fluids. The various bottles were so connected by rubber tubes, that the blood from each passed through a common outlet. This outlet tube was in the same way connected with the two inflow or venous canulas leading into the sinus. When different liquids were used, they were, of course, contained in separate Mariotte's flasks, carefully adjusted, so that the pressure under which the liquid flowed out of them was the same for all. In all the experiments on the heart, the "venous pressure" indicates the height above the heart of the bottom of the air-tube of the supplying Mariotte's flasks, expressed in c.m. The supplying-tubes of these flasks had stopcocks on them, by the closing and opening of which any one flask could be used to feed the heart.

The aortic or outflow canulas were all connected with a single tube, from the distal end of which the liquid pumped by the ventricle flowed out and was collected and measured at certain definite intervals. The height of the outlet of this tube is referred to in each experiment as the arterial pressure. A mercury manometer was also connected with the outflow tube near the heart, its pen writing on the smoked paper of a revolving drum on which also a chronograph recorded seconds.

As regards the experiments on the vessels, the method employed con-

sisted in cutting out the heart and inserting canulas into the aortic trunks and one canula into the sinus. The aortic canulas were connected with Mariotte's flasks, placed at a certain height above the body of the animal, from which flasks liquid was made to flow into the arteries. This liquid, after circulating through the capillaries and veins, was drained off from the sinus into a beaker and measured at definite intervals. After this outflow had become constant, circulating fluid plus the drug was substituted for the normal circulating fluid, and the action of the drug on the vessels determined from the change which took place in the amount of the outflow in a unit of time. A decreased outflow indicated increased resistance to the flow of the fluid through the vessels, or, in other words, a constriction of them, and an increased outflow, a dilatation of them. Parallel observations were made on both frogs and terrapins according to the methods thus briefly outlined.

Observations on bloodvessels were also made according to a method recently employed by Krüger, of Berlin, and of which a short account was found in the December number of the *Therapeutic Gazette* for 1885.

In these observations, the frogs were curarized just sufficiently to abolish all voluntary and reflex movements; the animal was then placed on a glass plate armed with a cork ring, on which the tongue was fastened with needles in the usual manner, so as to expose its under surface; being kept moist with normal salt solution, it was examined under the microscope with a magnifying power of sixty diameters. After selecting from the mass of bloodvessels a certain small vein, a capillary and an arteriole, the outlines of which were the most clearly defined, outline drawings of them were made through a camera (Oberhäuser's), and careful measurements of them taken in millimetres. All observations were confined to certain short sections of the vessels thus selected. During the first ten minutes several measurements were made and carefully compared, and when it was found that they became uniform, the drug was either injected into one of the lymph-sacs, or applied in solution or in substance to the surface of the tongue, a short distance away from the point which was directly under the objective, so as not to interfere with the clearness of the field. It was found best to select small sections of clear and well-defined vessels, and confine all subsequent observations and measurements to them, in order to insure uniformity. The drug once administered, drawings of the vessels were made every five minutes, carefully measured and recorded. As a rule, these observations were not continued much over an hour, and some of them had to be discontinued even before the end of that time for reasons hereafter to be stated.

Before, however, taking up the experiments on the heart and bloodvessels, it is perhaps best to consider here the few points ascertained with regard to the action of these drugs upon the blood itself.

The blood used in these experiments to feed the heart, after being isolated, was obtained from a slaughter-house in the immediate vicinity of Washington, and collected directly from the animal; while being drawn it was defibrinated and then put into a clean, dry glass bottle and brought home. The blood was used in from one hour to an hour and a half from the time of collection. At this time, the blood usually had a sort of venous color, and only when the animal had been killed according to the Jewish rite of cutting its throat without previously stunning it by a blow upon the head, did it retain its bright scarlet color up to the time it was used.

The blood obtained in this manner was filtered through a fresh, clean cloth and mixed with an equal quantity of Ringer's salt solution. After some shaking, the mixture generally assumes a bright scarlet color, and this color it retains, as a rule, from three to four hours, or even longer. This mixture is termed normal blood or normal blood mixture in the experiments.

The drugs employed were first dissolved in Ringer's saline and then mixed with the blood; this mixture is called "poisonous blood," or, according to the drugs mixed with it, kairinized or thallinized blood, and so on.

When, in this manner, a portion of the blood was kairinized in the proportions used in the experiments (0.03–0.05 gramme of kairin to 100 c. c. of blood mixture) the mixture quickly changed color, and, within twenty minutes, it had passed from a bright scarlet to an intense dark violet, almost black color. In the case of thallin, the color of the blood changed into a dark brown chocolate tint in about the same period. Hydrochinon changes the scarlet color of normal blood into a cherry-red, the difference being slight but perceptible.

While, then, kairin, thallin, and hydrochinon more or less darken the color of normal blood, the contrary is true of resorcin, which renders it of a slightly brighter red than normal. Besides, while normal blood mixture, as has been mentioned before, after shaking for a few minutes, retains its bright scarlet color for three or four hours, resorcinized blood will remain bright red for days. A small portion of resorcinized blood put into a test-tube and set aside, was found to begin changing its color slightly only after the third day.

Antipyrin does not seem to influence the color of the blood appreciably. but rather tends to preserve the bright red color than darken it.

This peculiar influence of kairin, thallin, and hydrochinon upon the color of the blood was also noticed in the experiments on the frog's tongue, but here it, of course, required a much longer time before it became apparent.

In order to test the influence of these drugs on the process of coagulation, advantage was taken of an observation frequently made while

operating on terrapins. The abdominal cavity of these creatures, as well as the pericardial sac, usually contains a rather large quantity of fluid of an alkaline reaction which has the property of hastening coagulation, and the clot produced by adding some of this fluid to the blood is normally of the consistence of soft jelly.

In one of these experiments, 12 clean watch-crystals were used, into 10 of which 2 c. c. of this abdominal lymph were carefully measured; 0.04 gramme of each of the drugs was then weighed out, and this quantity divided, so that for each drug there were two separate watch crystals containing the drug dissolved in 2 c. c. of the lymph. The 2 remaining crystals were reserved for normal blood, one containing lymph, the other being empty. The drugs having been dissolved in the lymph by gently stirring with a glass rod, a canula was now inserted into one of the arterial trunks of the heart, and the latter allowed to pump a certain quantity of blood into each of the watch crystals, which quantity, so far as could be judged, was about equal to that of the lymph containing the drug in solution. The result was, that in all except resorcin, coagulation took place much sooner in the crystals containing the drugs than in the one which contained normal lymph only, or in the one into which pure blood had been allowed to flow. In the crystals containing kairin, thallin, hydrochinon, and antipyrin, coagulation took place in from 8 to 12 minutes; in the remainder, it took half an hour. The clots produced by kairin, thallin, and hydrochinon were of a very dark brown color, and had the consistency of firm jelly; the other three were of a bright scarlet color. The driest and firmest clot was that which contained antipyrin.

It now remained to ascertain the action of these drugs upon the corpuscular elements of the blood. For this purpose, a small drop of blood was collected upon a clean slide, as it flowed from one of the arterial canulas. This blood was, in all cases, immediately mixed with an about equal quantity of a 2 per cent. solution of the drug in Ringer's saline, covered with a glass cover, and placed under the microscope, the preparation of a specimen occupying only a few seconds. As control specimens, several normal slides were prepared, consisting only of blood and Ringer's saline, in equal proportion. In these normally prepared specimens, the red blood-corpuscles appeared as oval flattened disks, of a light brownish-red color, no nucleus being at all discernible in them. The white corpuscles, much smaller than the red ones, still showed amœboid movements, and in some instances two were seen to fuse into one another; their contents were markedly granular, contrasting strongly with the uniform and homogeneous appearance of the red corpuscles.

In the kairinized specimen, the color of the red corpuscle was found to have entirely disappeared by the time the specimen was brought under the microscope, and a small, sharply defined, and granular nucleus

occupied the centre of the disk. The same change was found to have taken place in the thallin specimen. In the one with hydrochinon, these changes were much less marked; the color, although changed very slightly, was still that of a red blood-corpuscle, and the nucleus was never so well defined, nor so granular and round, as in the case of kairin and thallin. The resorcin specimen showed only a very faint and ill defined large and more oval nucleus within a somewhat indistinctly granular corpuscle; no change from this was noticed during half an hour's observation in any of the specimens. Antipyrin was found to have no appreciable influence upon the red corpuscles, while all the drugs promptly arrested all amœboid movements of the white corpuscles.

These few preliminary observations show quite sufficiently that kairin, thallin, hydrochinon, and antipyrin hasten the process of the coagulation of the blood, and that kairin, thallin, and perhaps, also, hydrochinon, have a destructive influence upon the hæmoglobin of the red blood-globules; they all arrest the movements of the white corpuscles.

I. Kairin.

The contributions to the literature on the physiological action of kairin, so far as I was able to find them, are few in number and limited in extent. Regarding its influence on the circulation, we hear from Queirolo (*Italia Medica*, No. 26, 1886) that under its influence the pulse-rate is lowered from six to eighteen beats per minute, according to the dose; that the arterial pressure is not appreciably affected, but is rather increased than diminished; and that its effect upon the heart is not sufficient to contraindicate its use. Girat (*Thèse de Paris*) finds a constant decrease in the frequency of the pulse and in the number of respirations; from his experiments he concludes that kairin reduces the temperature by its direct action upon the cellular tissues and by retarding the processes of combustion. De Renzi (*Rivista Klin. Terap.*, June, 1883) finds that kairin always diminishes the pulse-rate, and the sphygmograph shows an augmentation in the force of the cardiac contractions.

Regarding the influence of kairin upon the bloodvessels, Queirolo (*Arch. Ital. de Biologie*, fasc. ii. p. 224, 1884) states that he observed a notable dilatation of the peripheral bloodvessels; that in fever patients this dilatation precedes the fall in temperature for some time, and when the temperature rises again, the bloodvessels contract anew and the influence of the remedy passes off. Albertoni and Guaresch (*Centralblatt f. die ges. Therapie*, May, 1885) have arrived at the conclusions that kairin diminishes the frequency of the pulse-rate and causes a lowering in the blood-pressure, also that in small doses it increases the elimination of carbonic acid, diminishes it in large doses; the processes of combustion are retarded and the temperature is reduced by its diminishing influence on heat-production. Brouardel, Loye, and

Dujardin-Beaumetz, having observed the destructive influence kairin exerts upon the red blood-corpuscles, conclude that it reduces temperature primarily by diminishing the respiratory power of the red blood-corpuscles, destroying their hæmoglobin, and hence regard the remedy as dangerous and worthy of condemnation only.

In therapeutical literature a number of fatal cases of collapse, with intense cyanosis, have been reported, over which condition stimulants had no modifying influence. Unpleasant gastro-enteric symptoms, as vomiting and diarrhœa, also profuse sweating, are the almost invariable accompaniments of its administration in full doses. The small number of cases which have been recorded in which it had a more favorable effect seem only to increase, rather than diminish, the uncertainties of its action, and hence it is at least very doubtful that kairin will ever establish for itself a firm foothold among the remedies employed to reduce temperature in fever.

A. The Influence of Kairin on the Heart.

EXPERIMENT VI.—November 4, 1885. Frog 192 grms. Beef's blood and Ringer's saline (1 : 1½). Inflow canula in inferior vena cava. Outflow canulas in right and left aortæ. Venous pressure 5 c.m. Arterial pressure 15 c.m.

Time P.M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The injections of kairin and atropin into the inflow tubes were made at the time mentioned on the same line in the first column.
3.00	—	—	—	Frog in box.
30	44	30	25°	
35	44	30		
40	44	30		
45	45	29		
50	45	29		
55	45	29	25.6	
4.00	45	29		
05	45	29.5		
09	45	29.5		
13	45	29.5		
16	45	29.5	26	Injected 0.002 grm. of kairin into inflow tube; followed by almost instantaneous diastolic arrest of both auricles and ventricle; heart recovered on arterial pressure being lowered.
42	46	34		
45	47	34		
47	48	34.5		
50	48	34.5		
55	48	34.5	—	Injected 0.001 grm. of kairin; arrest transient, heart quickly and completely recovered.
5.00	46	35		
05	46	35		
10	46	34	27.2	Injected 0.002 grm. of kairin; no complete arrest, but blood ceased to come over; pressure lowered, and heart recovered.
15	46	34		
20	46	30		
25	47	32		

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The injections of kairin and atropin into the inflow tubes were made at the time mentioned on the same line in the first column.
5.26	43	30		
27	45	30		
30	47	32		
31	49	34		
33	49	34		
37	49	34	—	Injected 0.003 grm. of kairin.
38	41	17		
40	48	32		
45	48	32	—	Injected 0.003 grm. of kairin, and 0.003 grm. of atropin.
46	47	25		
47	48	32		
52	49	32		
57	49	32		
6.00	49	31	—	Injected same.
01	39	9		
02	49	30		
05	50	30		
10	49	30	—	Injected 0.003 of atropin.
11	49	30		
13	50	28		
15	50	28		
20	50	28	—	Injected 0.003 of kairin.
21	44	24		
22	50	28	—	Injected 0.003 of kairin.
23	30	12		
24	40	25		
30	50	28	—	Experiment ended.

EXPERIMENT V.—Nov. 3, 1885. Terrapin 1600 grms. Beef's blood and Ringer's saline (1 : 1½). Inflow canulas in inferior vena cava and right superior vena cava. Outflow canulas in pulmonary artery and right aorta. Venous pressure 6 c.m. Arterial pressure 22 c.m. Kairinized blood (*a*) contains 0.04 grm. of kairin to 100 c.c. of blood. Kairinized blood (*b*) contains 0.08 : 100.

Time P.M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	Kairinized blood was supplied to the heart at the time mentioned on the same line in the first column.
3.00	—	—	—	Terrapin in box.
40	36	27	17°	
44	36	27		
46	36	26	—	On kairinized blood (*a*) for one minute.
48	34	27		
50	32	33.5		
54	36	31		
57	36	30	—	On kairinized blood (*a*) for five minutes.
58	36	27		
59	34	30		
4.00	32	34		
01	32	36		
02	31	36		
05	25	50		
08	28	50	—	Ventricle shows increasing relaxation; its systole abnormally prolonged.
11	30	50		
13	32	54		
20	30	52		
23	30	52	—	On kairinized blood (*b*) for one minute.

Time P.M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	Kairinized blood was supplied to the heart at the time mentioned on the same line in the first column.
4.24	25	44	16°	Heart stopped in diastole; pressure lowered.
30	23	54	—	Heart resumed work; rate still low.
35	25	50		
40	26	50		
43	26	50	—	On kairinized blood for half a minute.
44	—	—	—	No blood coming over; heart's action peristaltic; lowered arterial pressure, and drained off kairinized blood.
48	25	55	—	Heart resumed work; ventricle very large, its systole abnormally prolonged, hence increase in the amount of work done.
51	25	62		
56	26	60		
59	26	60		
5.00	26	52		
05	26	55		
10	28	55	17	
15	28	55		
25	30	52		
28	30	50	—	Injected 0.01 grm. of atropin.
30	36	40		
32	36	35	—	On kairinized blood for two minutes.
35	40	23	—	15 minutes after this observation was taken, blood ceased to come over, heart's movement peristaltic; recovery took place.
40	29	35		
44	29	45		
49	30	52		
53	33	44		
59	32	53		
6.05	35	50	—	Heart's action becoming irregular. Experiment ended.

B. The Influence of Kairin on the Bloodvessels.

EXPERIMENT XX.—Nov. 21, 1885. Terrapin 1205 grms. Ringer's saline. Inflow canulas in right and left aortic trunks. Outflow canulas in sinus. Venous pressure 0. Arterial pressure 16 c.m. Brain and cord destroyed. Constant pressure. Kairinized saline contains 0.005 : 100; in latter part 0 01 : 100.

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow per min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in the second column.
3.20	—	—	—	—	Terrapin in box.
50	3.52	19°	16	8	
52	54	—	16	8	
54	56	—	16	8	
56	58	—	16 5	8.2	
58	4.00	—	16.5	8.2	
4.00	02	—	15	7.5	
02	04	—	15	7.5	
04	06	—	15	7.5	
06	08	—	16.5	8.2	
08	10	—	16.5	8.2	
10	12	—	17	8.5	
12	14	—	17	8.5	On kairinized saline for two min.
14	16	—	14	7	

Time P.M. From	to	Temp. Cent.	Total outflow.	Outflow per min.	The circulating fluids were supplied to the vessels at the time mentioned on the same line in the second column.
4.16	4.18	—	18	9	
18	20	—	24	12	
20	22	—	28	14	
22	24	—	16	8	
24	26	—	15	7.5	On kairinized saline for four min.
26	28	—	10	5	
28	30	—	16	8	
30	32	—	30	15	
32	34	—	25	12.5	
34	36	—	17	8.5	
36	38	—	15	7.5	
38	40	—	16	8	On kairinized saline for four min.
40	42	—	13	6.5	
42	44	—	16	8	
44	46	18°	32	16	
46	48	—	24	12	
48	50	—	14	7	
50	52	—	13	6.5	
52	54	—	13	6 5	
54	56	—	13.5	6.7	On kairinized saline for six min.
56	58	—	14	7	
58	5.00	—	23	11.5	
5.00	02	—	27	13.5	
02	04	—	28	14	
04	06	—	18	9	
06	08	—	15	7.5	On kairinized saline for six min.
08	10	—	18	9	
10	12	—	30	15	
12	14	—	44	22	
14	16	—	40	20	
16	18	—	24	12	
18	20	—	18	9	On kairinized saline for eight min.
20	22	—	22	11	
22	24	—	30	15	
24	26	—	38	19	
26	28	—	44	22	
28	30	—	45	22.5	
30	32	—	48	24	
32	34	—	30	15	
34	36	—	24	12	
36	38	—	20	10	
38	40	—	18	9	On kairinized saline for eight min.
40	42	—	25	12.5	
42	44	—	34	17	
44	46	—	44	22	
46	48	—	50	25	
48	50	—	46	43	
50	52	18	40	20	
52	54	19	33	16.5	
54	56	—	28	14	
56	58	—	26	13	
58	6.00	—	26	13	Experiment ended.

EXPERIMENT LX.—January 8, 1885. Frog 104 grms. Curarized. Tongue under microscope magnified 60 diameters. Measurement of vessels made from camera drawings, stated in μ.

Time P. M.	Art.	Calibre of Cap.	Veins.	Remarks.
3.30	4.6	1.0	6.4	
35	4.6	1.0	6.6	Applied 5 drops of 2 per cent. solution of kairin to surface of tongue.
39	5.4	1.8	10.6	
42	5.8	2.2	13 6	
46	6.2	2.8	14.2	
50	6.6	2.6	14.6	Washed away kairin with normal salt solution.
53	6.4	2.0	14.8	
58	6 2	2 0	15.2	
4.05	6.0	2.0	14.2	
10	6 0	1.5	14.6	
15	5 8	1.2	14.6	
20	5.4	1.0	13.4	
25	5.2	1.0	12.8	
30	5.0	1.0	11.2	
35	5.0	1.0	10.8	
40	4.8	1 0	10.2	
45	4.6	1.0	10.2	Circulation still very brisk in all the vessels. Experiment ended.

Experiment VI. shows that kairin, in comparatively small doses, lowers the rate of the heart and the work done; in larger doses it causes diastolic arrest of both auricles and ventricle; atropin, although seemingly retarding this result, is not entirely able to prevent its occurrence.

Experiment V. shows that kairin, in small doses, lowers the rate of the heart but increases the work done; larger doses decrease both rate and the amount of work done; still larger doses cause diastolic arrest of the whole organ; after atropinizing the heart, kairin seems to increase the rate of the heart in small doses, at the same time decreasing the work done; atropin considerably antagonizes the action of kairin upon the rate, and the work done in the case of the terrapin.

A strong solution of kairin injected into the substance of the ventricle causes immediate systolic arrest of the heart of the frog and terrapin.

Experiment XX. shows a slight initial decrease in the amount of outflow during the first few observations, denoting a certain degree of contraction, which rapidly gives way to a dilatation of the arterioles and capillaries. This is a constant occurrence in all the experiments made with regard to this point. The temporary contraction is entirely wanting in the subsequent observations, when dilatation is produced directly after the admission of kairinized saline into the vessels.

In the beginning of this experiment on the vessels, the great veins adjoining the sinus could be seen contracting very regularly; their contractions diminished in frequency after the first few observations with kairinized saline, and ceased altogether while the third observation was taken. The sinus kept on contracting all through the experiment, but

while under normal saline the contractions numbered thirty-two per minute in the beginning, they numbered only four per minute at the close.

Experiment XII. on the frog's tongue, shows that kairin promptly causes a very considerable dilatation of the veins and capillaries, which dilatation exceeds that of the arterioles; it shows also that the capillaries and arterioles recover their normal calibre long before the veins do, a point of some importance.

Four experiments were made with kairin on the frog's tongue, from which this is selected as typical, and as showing all the principal points. When kairin was injected into one of the lymph-sacs in doses of 0.03 gramme, the veins and capillaries became promptly dilated; the arterioles, on the contrary, showed in three cases out of four a slight initial contraction preceding dilatation, and in two cases contraction following dilatation. In no case, however, whether kairin was injected or applied externally in solution, did the arteries show the same prompt and extensive dilatation as did the veins; the veins never returned to their normal calibre as quickly as the arteries and capillaries. When kairin was applied to the tongue in the form of a saturated solution, or in crystals, the tissues were destroyed; the veins, capillaries, and arterioles contracted, and shortly after that they disappeared altogether, and in their places appeared narrow chains of fibrous tissue. Toward the end of an experiment, in which the circulation had become sluggish, and kairin had been applied pretty freely, the veins and their contents had assumed an intense dark violet hue. The arteries and capillaries had remained free from this, apparently indicating a certain affinity of kairin for veins and venous blood. To the naked eye, the tongue looked as if the vessels had been traced out in violet ink.

On several occasions a distinct acceleration of the blood flow in the arterioles was noticed as following the injection of kairin into one of the lymph-sacs; the flow in the veins was slowed.

The conclusions which we may draw from this and other experiments on the frog's tongue with kairin are: (1) that it produces dilatation of the capillaries and veins, which dilatation much exceeds that of the arterioles, which latter is sometimes preceded, sometimes followed, by an abnormal contraction; (2) that it causes a slight acceleration in the current in the arterioles and a slowing of the flow in the small veins.

All the experiments made with kairin on the heart (nine in number), show the great weakening effect it exerts upon the contracting power of the cardiac muscle. In some cases in which this organ happened to be in unusually good working order, and low venous as well as arterial pressure was used, a very slight but transient increase in the rate, and even in the force of its contraction was noticed when the dose was not too large; but this was always quickly followed by signs of general weakening. The entire organ, then, becomes much enlarged, occupying

from twice to thrice its normal volume, its contractions become peristaltic, incomplete, and sluggish; the auricles keep well filled with blood, never emptying themselves completely. As a rule, the auricles are much sooner affected and recover much later than the ventricle. Under these circumstances the rate of the heart is much decreased, the amount of work done is sometimes increased, owing to the relaxed condition of the ventricle, but more often decreased, and, finally, diastolic arrest ensues. The heart presents the color of kairinized blood, which, however, again disappears, but, after repeated kairinization, it becomes permanent—in other words, the color of the blood has become the color of the muscular substance of the heart. From this condition the heart was never found to recover: the organ seems as if gelatinized, moves *in toto*, shrinks, and contracts little by little, responds to neither mechanical nor electrical stimulation, and is to all appearances dead. This condition of the heart may almost at once be produced by injecting a two per cent. solution of kairin into its substance, by which arrest in systole is produced.

The temporary diastolic cardiac arrest which kairin produces is most probably due to its stimulating effect on the terminal filaments of the pneumogastric, and the vascular dilatation to a similar influence on the ganglia of the vaso-dilators. Kairin must also be considered a muscle poison.

From the results of all these experiments, it is quite clear that kairin reduces temperature, both by diminishing heat production and by increasing heat radiation. The distinctive influence it exerts on the red blood-corpuscles, however, and the weakening effect upon the heart, render its employment objectionable and dangerous.

II. Thallin.

The literature on the physiological action of thallin is still more scanty than that of kairin. The only physiological work that I have been able to consult was by Maragliano (*Gazz. d. Osp.*, Milan, 1885, vi. 425–427). According to him, thallin causes a rise, afterward a fall, in the arterial pressure, which fall is attributed to its weakening influence upon the heart, and also to the dilatation it produces in the cutaneous vessels. The frequency of the pulse, as well as that of the respirations, is diminished. By means of the plethysmograph of Mosso, and the calorimeter of Winternitz, Maragliano found that thallin caused considerable dilatation of the cutaneous bloodvessels, which dilatation went hand in hand with the fall in temperature, and the radiation of heat increased as the vessels dilated. The amount of urea and carbonic acid eliminated was found to be diminished. The conclusions at which he arrived were that thallin lowers the temperature by directly diminishing the respiratory capacity of the blood, hence retarding the processes of combustion.

According to Dujardin-Beaumetz (*Therap. Gaz.*, September, 1885), thallin, like kairin, lowers the temperature, not by its influence on the heat centres, but by directly diminishing the respiratory power of the blood and by dissolving out its hæmoglobin. He mentions the case of a tuberculous patient who had received but one gramme of thallin during twenty-four hours. The temperature fell to 89.6° F., and the most strenuous efforts were required to arouse this patient from the state of collapse into which he was plunged.

The cases which have so far been recorded, however, are much more favorable to thallin as an antipyretic likely to have a future than are those of kairin. Alexander (*Centralblatt f. klin. Med.*, Leipsig, 1885, vi. 89–93) used thallin in fourteen cases of febrile disease, and noticed chills and vomiting to occur but once; therefore he was led to consider thallin one of the most valuable of antipyretics, being superior to kairin, though inferior to antipyrin.

According to Mingazzini (*Gazz. d. Osp.*, No. 14, 1885), thallin, as an antipyretic, is superior to both kairin and antipyrin, although hardly to be preferred to the latter.

A. Influence of Thallin on the Heart.

EXPERIMENT VII.—November 6, 1885. Frog 135 grms. Beef's blood and Ringer's saline (1 : 1½). Inflow canula in inferior vena cava. Outflow canulas in two aortic trunks. Venous pressure 2.5 c.m. Arterial pressure 20 c.m.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	Injections of thallin were made into one of the inflow tubes at the time mentioned on same line in first column.
3.25	—	—	—	Frog in box.
55	52	18	26°	
58	52	18		
4.02	52	18.5		
05	52	18.5		
10	52	18	—	Injected 0.005 grm. of thallin.
11	54	16		
12	52	16		
13	52	14	—	Injected 0.01 grm. of thallin.
17	52	14		
18	50	8		
19	50	10	25.2	Auricles three times their normal size, and almost entirely inactive; ventricle larger than normally, contracting incompletely.
25	52	10	—	Injected 0.01 grm. of thallin.
26	50	9		
27	48	8		
29	46	6		
35	44	3		
37	42	2		
42	33	0	—	Heart arrested in diastole.
5.30	—	—	24.6	Heart much smaller than at last observation. Experiment ended.

EXPERIMENT XXXVIII.—December 21, 1885. Terrapin 930 grms. Beef's blood and Ringer's saline (1 : 1). Inflow canulas in hepatic vein and inferior vena cava. Outflow canulas in right aorta and pulmonary artery.

Venous pressure 7 c.m. Arterial pressure 24 c.m. Thallinized blood contained 0.1 grm. of thallin in 100 c.c. of normal blood mixture; atropinized blood 0.01 grm. : 100 c.c.

Time P M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in the first column.
3.05	—	—	18°	Terrapin in box.
20	25	29.5		
25	25	29.5		
30	25	29		
35	25	29		
40	25	28.5	—	On thallinized blood.
41	27	32		
42	22	30		
43	20	30		
44	18	32		
45	16	30		
46	14	32	—	Auricles 3 to 4 times their normal size; rosy, dark-colored, and contracting imperfectly.
47	14	35		
48	12	36	—	Ventricle much relaxed, contracting sluggishly but completely; cardiac systole abnormally prolonged; on normal blood mix-
51	18	54	19	[ture.
53	25	40		
56	25	36	—	On thallinized blood.
4.00	25	38		
01	22	33		
03	16	19	—	Auricles continue full and large; ventricle large, contractions peristaltic and far from
05	16	15		[complete.
07	8	13		
10	7	13		
12	7	13	—	On normal blood mixture.
13	9	22		
15	19	38		
17	22	30		
21	25	25	—	Ventricle beginning to resume its normal dimensions; auricles continue same as previously noted.
4.25	25	22	20	On atropinized blood.
26	25	23		
28	25	25		
30	27	28		
31	27	30	—	On thallinized blood.
33	18	28		
37	18	21.5	—	Entire heart very weak and beginning to grow smaller.
40	17	26		
45	8	17	—	On normal blood mixture.
48	8	18		
52	15	25	—	On thallinized blood.
55	14	14		
5.00	14	10		
05	13	5		
10	11	2	—	This observation was followed by temporary diastolic arrest; on normal blood.
19	25	44		
25	21	21		
30	24	22	—	Ventricle almost completely recovered.
35	24	21	20	Auricles paralyzed beyond recovery. Experiment ended.

B. Influence of Thallin on the Bloodvessels.

EXPERIMENT XXXIV.—December 14, 1885. Terrapin 740 grms. Ringer's saline. Inflow canulas in right and left aortæ. Outflow canula in sinus. Arterial pressure 10. Venous pressure 0. Thallinized saline used in two different proportions, viz., (*a*) 0.1 grm.: 100 c.c.; (*b*) 0.15 grm.: 100 c.c.

Time P. M. From	Time P. M. to	Temp. Cent.	Total outflow.	Outflow per min.	The circulating fluids were supplied to the vessels at the time mentioned on same line in second column.
3.20	3.56	20.4°	—	—	Terrapin in box.
56	58	—	9	4.5	
58	4.00	—	10	5	
4.00	02	—	11	5.5	
02	04	—	10.5	5.2	
04	06	—	11	5.5	
06	08	—	11	5.5	
08	10	—	10.5	5.2	On thallinized saline (*a*).
10	13	—	16	5.3	
13	16	—	18.5	6.2	
16	18	—	22.5	11.2	Off thallinized saline; on normal.
18	20	—	27	13.5	
20	22	20.6	26	13	
22	24	—	22	11	
24	26	—	18	9	
26	28	—	16	8	
28	30	—	14	7	
30	32	—	14	7	On thallinized saline (*a*).
32	34	—	15	7.5	
34	36	—	18	9	
36	38	—	20	10	
38	40	—	24	12	Off thallinized saline; on normal.
40	43	—	35	11.6	
43	45	—	18	9	
45	47	—	15	7.5	
47	50	—	19	6.3	
50	52	—	12	6	
52	54	—	12	6	On thallinized saline (*a*).
54	57	—	21	7	
57	59	—	22	11	
59	5.01	—	24	12	
5.01	03	—	30	15	
03	05	—	32	16	Off thallinized saline (*b*); on normal.
05	07	—	36	18	
07	09	—	30	15	
5.09	5.11	21	21	10.5	
11	13	—	16	8	
13	15	—	14	7	
15	17	—	12	6	
17	19	—	14	7	On thallinized saline (*b*).
19	21	—	18	9	
21	23	—	20	10	
23	25	—	25	12.5	
25	27	—	27	13.5	Off thallinized saline; on normal.
27	29	—	27	13.5	
29	31	—	25	12.5	
31	33	—	22	11	
33	35	—	18	9	
35	37	—	16	8	
37	37	—	15	7.5	
39	41	—	15	7.5	
41	43	21.4	15	7.5	Experiment ended.

EXPERIMENT XLV.—January 2, 1886. Frog 65 grms.; curarized. Tongue observed under microscope magnifying 60 diameters. Measurements of vessels made from camera drawings, stated in μ.

Time A. M.	Art.	Calibre of Cap.	Vein.	Remarks.
10.35	2.8	1.0	5.0	
40	2.8	1.0	5.2	Injected 0.03 grm. of thallin into lymph-sac.
45	3.6	2.0	8.2	
50	3.5	2.2	10.6	
55	3.0	2.2	7.8	Velocity of current apparently quickened in arterioles, slowed in veins.
11.00	3.0	2.2	6.6	
05	2.8	2.0	6.8	
10	2.6	2.0	7.0	
15	1.8	2.0	7.4	
20	1.5	2.0	7.2	Color of blood, especially in veins, dark brown.
30	2.8	2.0	6.5	
40	3.0	1.8	6.4	Experiment ended.

Experiment VII. shows (1) that thallin, in very small doses, temporarily increases the rate of the heart, and only very slightly decreases the work done; (2) in larger doses it decreases both the rate and work, but influencing the latter more than the former; (3) in the largest doses it arrests the heart in diastole.

As to time and degree, thallin affects the different parts of the heart as follows: first, the sinus and great veins adjoining it; second, the auricles; and, lastly, the ventricle. The dose of thallin required to produce cardiac diastolic arrest is about five times as large as that of kairin, producing a similar result.

Experiment XXXVIII. admits of the following conclusions: 1. Thallin, in comparatively small doses, slightly increases the rate of the heart, and considerably increases the work done. 2. Larger doses decrease both the rate and the work done, finally producing diastolic arrest. 3. Atropin retards, but is unable to prevent this result. 4. Repeated thallinization of the heart is followed by a peculiar shrinkage of the entire organ, during which it presents the dark color of thallinized blood. 5. The order in which the different parts of the heart are affected is the same for the terrapin as for the frog. To this must be added that the injection of a 1 per cent. solution of thallin into the substance of the ventricle produces systolic arrest within a few minutes.

From Experiments XXXIV. and XLVII., on the bloodvessels, we may conclude (1) that thallin, in comparatively small doses, produces dilatation of the arterioles, followed by a contraction of the same; (2) it produces dilatation of the capillaries; (3) it causes a much greater and much more permanent dilatation of the small veins than of either

the capillaries or arterioles; (4) under thallin venous blood and the walls of the veins assume an abnormally dark color.

Summing up the results of all these experiments with thallin upon the heart and bloodvessels of the frog and terrapin, we notice, first, the striking similarity which exists between it and kairin, the only difference, in fact, being that thallin has a much less injurious influence upon the ventricle, the auricles and bloodvessels being equally affected by both drugs.

The temporary diastolic cardiac arrest produced by both these drugs, we are inclined to attribute for the most part to their stimulating influence on the terminal filaments of the pneumogastric. The dilatation of the bloodvessels, most probably, is produced by their stimulating effect upon the ganglia of the vasodilators. The subsequent contraction of both heart and arterioles is due to their direct action upon the muscular substance.

Thallin, like kairin, reduces temperature by diminishing heat production, and by increasing heat radiation; as an antipyretic it is less dangerous, but no less objectionable, than kairin, for while its effect upon the ventricle of the heart is less depressing than that of kairin, its influence upon the blood-corpuscles is sufficient to condemn it.

III. Hydrochinon.

According to Brieger (*Arch. f. Anat. u. Phys.*, 1879), hydrochinon produces dilatation of the arterioles and considerable lowering of blood-pressure. The dose required to reduce the temperature caused no change in rhythm, but sometimes a slight decrease in the rate; the pulse, however, became unusually small and soft, and shortly thereafter collapse ensued, the heart-sounds became inaudible, and the impulse of the heart could not be felt. Brieger also found that hydrochinon had a paralyzing influence upon the frog's heart, especially its muscular substance. The heart ganglia, according to Brieger, are only weakened by strong doses, and not at all affected by small ones.

Seifert (*Berl. klin. Woch.*, 1884, xxi. 450–452) recommends hydrochinon as safe and prompt in its action, its administration being accompanied by but slight disturbances; the cerebral symptoms of typhoid patients were very much improved by its use. From the account which Seifert gives us, we take it that hydrochinon, though lowering the pulse-rate at the same time that it reduces the temperature, slightly increases arterial tension, or, at least, does not lower it under doses which are sufficient to cause a fall in the temperature.

A. Influence of Hydrochinon on the Heart.

Experiment XL*a*.—December 22, 1885. Frog 280 grms. Beef's blood and Ringer's saline (1:1). Inflow canula in inferior vena cava. Outflow canulas in two aortic trunks. Venous pressure, at start, 6 c.m. Arterial

pressure 12 c.m. Hydrochinon blood (*a*) contained 0.1 grm. in 100 c.c. of normal blood mixture; Hydrochinon blood (*b*) 0.2 : 100 c.c.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on same line in first column.
2.30	—	—	—	Frog in box.
3.00	42	22	23°	
05	42	22.5		
10	43	22	—	Venous pressure lowered to 2.5 c.m.
15	43	15		
20	43	15		
25	43	15	—	On hydrochinon blood (*a*).
26	43	16		
27	40	15.5		
28	39	15		
29	39	14.5		
30	37	13	—	Heart larger, and contracting less perfectly than normally.
31	36	13		
32	36	12		On normal blood mixture.
35	38	15	24	
37	40	15		
40	40	15	—	Venous pressure raised to 5 c.m.
45	42	23		
47	42	22.5		
50	42	22	—	On hydrochinon blood (*b*).
52	36	7	—	Great veins, sinus, and auricles quickly paralyzed; three times their normal size; contractions barely perceptible; ventricle much weakened, though still contracting.
53	—	—	—	Blood ceased to come over; venous pressure lowered to 2.5 c.m.
56	21	1		
4.02	32	7		
07	32	7		
15	36	7		
25	40	8.5	25	Ventricle completely recovered; condition of great veins, sinus, and auricles same as previously noted, and apparently beyond recovery. Experiment ended.

EXPERIMENT XXXII.—December 11, 1885. Terrapin 1450 grms. Sheep's blood and Ringer's saline (1 : 1½). Inflow canulas in inferior vena cava and left superior vena cava. Outflow canulas in pulmonary artery and right aorta. Venous pressure 6 c.m. Arterial pressure 18 c.m. Hydrochinonized blood(*a*) contained 0.05; (*b*) 0.1 grm. of hydrochinon in 100 c.c. of normal blood mixture.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on first line in first column.
3.00	—	—	—	Terrapin in box.
20	26	19	20°	
25	26	18.5		
30	27	18.5		
35	27	18.5		
40	27	18		
45	27	18.5	—	On hydrochinon blood (*a*).
50	25	19		
55	24	22	21	Auricles overdistended; ventricle normal; on normal blood.
4.00	25	19		
05	26	20		

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on first line in first column.
4.10	26	20.5	—	On hydrochinon blood (*b*); auricles still in a passive and overdistended condition.
11	26	20		
13	24	23		
14	12	15	—	Auricles and sinuses as above noted; ventricle greatly relaxed; its diastole prolonged; on normal blood mixture.
16	7	13		
18	9	13		
19	11	15		
21	23	30		
30	25	25	21.2°	
35	25	23	—	On hydrochinon blood.
36	25	25		
38	12	12	—	On normal blood mixture.
39	8	8		
40	10	10	—	Condition of heart as previously noted.
45	19	11		
50	24	22	—	Ventricle recovered but discolored; sinus, veins, and auricles paralyzed beyond recovery.
55	26	20	—	
5.00	26	18	21.6	Experiment ended.

B. Influence of Hydrochinon on the Bloodvessels.

EXPERIMENT XLVI.—December 26, 1885. Terrapin 980 grms. Inflow canulas in right and left aortic trunks. Outflow canulas in sinus. Arterial pressure 13 c.m. Venous pressure 0. Hydrochinonized saline (*a*) contained 1 grm. of hydrochinon : 500 of saline; (*b*) 2 grms. : 500 c.c.; (*c*) 3 grms. : 500 c.c.

Time P. M. From	Time P. M. to	Temp. Cent.	Total outflow.	Outflow per min.	The circulating fluids were supplied to the vessels at the time mentioned on same line in second column.
2.40	3.10	—	—	—	Terrapin in box.
3.10	3.12	16°	29	14.5	
12	14	—	31	15.5	
14	16	—	32	16	
16	18	—	33	16.5	
18	20	—	32	16	
20	22	—	31	15.5	On hydrochinon saline (*a*).
22	24	—	28	14	
24	26	—	21	10.5	
26	28	—	12	6	
28	30	—	10	5	
30	32	—	14	7	
32	34	17	12	10.5	
34	36	—	27	13.5	
36	38	—	30	15	
38	40	—	36	18	
40	42	—	37	18.5	
42	44	—	42	21	
44	46	—	56	28	On normal saline.
46	48	—	60	30	
48	50	—	52	26	
50	52	—	50	25	
52	55	—	70	26	
55	58	—	65	21.6	
58	4.03	—	90	19	
4.03	05	18	30	15	On hydrochinon saline (*b*).
05	07	—	31	15.5	

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow per min.	The circulating fluids were supplied to the vessels at the time mentioned on same line in second column.
4.07	4.09	—	28	14	
09	11	—	31	15.5	
11	13	—	35	17.5	
13	15	—	38	19	
15	17	—	43	21.5	
17	19	—	45	22.5	
19	22	—	75	25	
22	24	—	52	26	
24	26	—	58	29	On normal saline.
26	20	—	48	24	
28	30	19°	45	22.5	
30	32	—	44	22	
32	34	—	44	22	
34	38	—	78	19.5	
38	41	—	63	21	
41	43	—	42	21	
43	45	—	41	20.5	On hydrochinon saline (*c*).
45	47	—	45	22.5	
47	49	—	47	23.5	
49	51	—	55	27.5	
51	53	—	58	29	
53	55	—	58	29	
55	57	—	60	30	On normal saline.
57	59	—	51	25.5	
59	5.01	—	42	21	
5.01	03	—	38	19	
03	05	—	37	18.5	
05	07	—	36	18	
07	09	—	35	17.5	
09	11	—	35	17.5	
11	13	20	36	18	Experiment ended.

EXPERIMENT XL β.—December —, 1885. Frog 64 grms; curarized. Tongue, under microscope magnifying 60 diameters. Measurements of vessels made from camera drawings, stated in μ.

Time P. M.	Calibre of Art.	Cap.	Vein.	Remarks.
2.30	4.4	0	5.2	No capillaries apparent.
35	4.4	0	5.4	Injected 0.03 of hydrochinon into lymph-sac.
40	4.6	1.5	7.2	Capillaries abundant.
45	4.6	1.5	8.4	
50	4.6	1.5	9.0	
55	4.6	1.5	9.2	Velocity of current quickened in arterioles, slackened in veins.
3.10	4.4	1.2	9.0	
20	4.4	1.2	7.5	
35	4·4	1.2	7.4	Applied 5 drops of one per cent. solution of hydrochinon in saline to surface of tongue.
42	4.6	2.0	8.0	
50	4.8	2.0	9.6	
55	4.4	2.0	9.4	Washed away hydrochinon with salt solu-
4.00	4.0	2.0	8.4	[tion
10	3.6	1.5	8.6	
20	3.2	1.2	8.8	
25	3.2	1.0	8.6	Circulation still brisk in arterioles, abnormally slow in veins.
30	3.4	1.0	8.6	Experiment ended.

Experiment XLα. shows (1) that small doses of hydrochinon, in the frog, reduce the rate of the heart and the amount of work done; (2) that larger doses quickly paralyze the great veins, sinus, and auricles in the order in which they are named, while the ventricle is affected but slightly; (3) increasing venous pressure will materially hasten this occurrence.

Experiment XXXII. shows (1) that, in the terrapin, small doses of hydrochinon slightly increase the amount of work done by the heart, but reduce its rate; (2) larger doses rapidly reduce both rate and work, finally arresting the auricles and sinus in diastole, the ventricle, though much weakened, not being affected to that extent; the ventricle recovers quickly and completely, the auricles slowly and imperfectly.

In both the frog and the terrapin the great venous trunks adjoining and communicating with the sinus may be dissected out at some distance from the latter and canulas tied in, so that these veins remain in sight during the whole experiment. Under normal conditions, and as a sign that the venous pressure has been duly proportionate to the capabilities of the heart under observation, cardiac systole may be observed to start with a contraction of these veins, the contraction-wave travelling through the intervening structures until it reaches the ventricle; their contractions, in most cases, are as perfect and complete as are those of the auricles or ventricle. The same blood which flows into the sinus and then runs through the heart, also passes into these veins, and therefore the influence of poisoned blood on them can be observed as well as upon the other structures.

Experiment XLVI. shows that hydrochinon causes at first a contraction, followed by a dilatation of the arterioles and capillaries; large doses seem at once to dilate these vessels.

Experiment XLβ. shows (1) that hydrochinon produces dilatation of the arterioles and capillaries, which dilatation is followed by an abnormal contraction; (2) that it causes dilatation of the small veins, which dilatation is much more extensive and lasting than that of either the capillaries or arterioles; (3) it quickens the flow in the arterioles and slows it in the veins; (4) it imparts a deep purplish color to the blood flowing in the veins; (5) the effect is the same, whether hydrochinon is injected hypodermatically or is used externally; when injected, muscular twitchings come on, which necessarily interfere with the study of the vesssels of the tongue.

From all these experiments made with hydrochinon on the heart and bloodvessels of the frog and terrapin, we must arrive at the conclusion that it reduces temperature mainly by increasing heat radiation, owing to its influence upon the veins, which it largely dilates, and the capillaries and arterioles, which it also dilates, though to a less extent. Through

its influence upon the red blood-corpuscles it probably also diminishes heat production, by an impairment of their respiratory capacity.

The singular but noteworthy fact, observed under the microscope on the frog's tongue and elsewhere, that kairin, thallin, and also hydrochinon change the color preferably of venous blood, seems to point to a peculiar affinity of these substances for such blood, and it is not at all unlikely that the presence of carbonic dioxide in venous blood is the cause of its chemical decomposition underlying the appearance of this phenomenon. The peculiar coloring principle thus set free diffuses itself through the walls of the veins into the neighboring tissues.

When we now compare the action of hydrochinon upon the heart and the bloodvessels of the frog and terrapin, with that of kairin and thallin, the result shows that hydrochinon affects the ventricle of the heart still more favorably than thallin; the auricles, however, are as promptly paralyzed by hydrochinon as they are by thallin, and even kairin. All three largely dilate the veins, for which they show a decided preference, and they also dilate the capillaries and arterioles; the dilatation of the latter, however, is either preceded or followed by an abnormal contraction, especially noticeable when the drug was injected hypodermatically. On hypodermatic injection of all three of the drugs, slight muscular spasm may be seen on the frog's tongue.

The action of hydrochinon, then, being similar to that of kairin and thallin so far as the heart and bloodvessels are concerned, the explanation of its action must, in like manner, be similar (see page 387). The peculiar affinity of kairin, thallin, and hydrochinon for veins and venous blood cannot be explained by these experiments.

IV. Resorcin.

Comparatively little is known about the physiological action of resorcin on the circulatory apparatus. Russo-Giliberti, by means of the cromocitometer of Bizzozero, ascertained that resorcin temporarily increases the hæmoglobin of the blood; he also found that it decreases the elimination of carbonic acid. (*Arch. p. l. Sc. Med.*, Torino, 1883–84, vii. 171–186.)

Resorcin is said to possess decided antiseptic properties, and has frequently been recommended in putrid affections of the naso-pharynx and genito-urinary organs. In fever patients it reduces the temperature in doses of 1.5 gramme, but 3 grammes are often found necessary. A full dose of the drug is generally followed by dizziness, ringing in the ears, reddening of the face, an acceleration of the respiratory movements, and also the pulse-rate; the cutaneous vessels are congested, and the whole surface is bathed in perspiration. Dujardin-Beaumetz found intense visceral, and especially pulmonary, congestion in animals killed by resorcin, and does not recommend its employment as an antipyretic.

A. Influence of Resorcin on the Heart.

EXPERIMENT X.—November 10, 1885. Frog 110 grms. Beef's blood and Ringer's saline (1 : 1). Inflow canula in inferior vena cava. Outflow canulas in right and left aortæ. Venous pressure 3.5 c.m. Arterial pressure 20 c.m. Solution of resorcin used for injection into inflow tube containing 1 grm. : 50 c.c.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	Injections made at time mentioned on same line in first column.
2.30	—	—	—	Frog in box.
3.10	48	14.5	25°	
15	48	14.5		
20	48	15.5		
25	48	16		
30	48	15.5	—	Injected 0.01 grm. of resorcin.
34	48	15	24	
36	48	15	—	Injected 0.02 grm. of resorcin.
38	46	13.5		
40	46	14		
45	46	15	—	Injected 0.04 grm. of resorcin.
45^{20}	—	—	—	Complete diastolic arrest of both auricles and ventricles; applied atropin in solution (1 : 500) to surface of ventricle.
55	40	18	23	
4.00	42	15	—	Recovery of all parts of heart perfect.
05	42	15		
13	43	14		
16	45	14	—	Injected 0.04 grm. of resorcin.
17	42	5	—	Auricles distended and motionless; ventricle unaffected.
18	42	10		
25	44	13.5	—	All parts of heart recovered.
35	45	13.5	22	Injected 0.05 grm. of resorcin. After 20 contractions, diastolic arrest of the whole heart occurred; pressure lowered.
42	40	10	—	Auricles seem permanently affected; ventricle completely recovered.
52	43	10		
5.00	45	8	—	Experiment ended.

EXPERIMENT XIX.—November 20, 1885. Terrapin 940 grms. Beef's blood and Ringer's saline (1 : 1½). Inflow canulas in left superior and inferior venæ cavæ. Outflow canulas in right and left aortæ. Venous pressure 3 c.m. Arterial pressure 20 c.m. Resorcinized blood contains 1 grm. of the drug in 500 c.c. of normal blood mixture.

Time P.M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	Circulating fluids were supplied to heart at time mentioned on same line in first column.
3.15	—	—	—	Terrapin in box.
55	33	22	23°	
4.00	32	22		
10	33	22		
24	33	22	—	Raised venous pressure to 7 c.m.
25	34	45		
26	34	46	—	Lowered venous pressure to 3 c.m.
30	33	23	—	On resorcinized blood for one minute.
31	34	20.5		
32	34	16.5	—	Sinus and auricles large and overdistended; their contractions much weakened; ventricle not affected.

Time P.M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	Circulating fluids were supplied to heart at time mentioned on same line in first column.
4.33	33	16		
35	33	17.5		
39	33	21	24°	
41	33	20.5	—	Heart in normal working order.
43	33	20	—	On resorcinized blood for two minutes.
45	34	12		
47	35	7		
49	35	4	—	Great veins, sinus, and auricles paralyzed; ventricle but slightly weakened.
53	35	12		
57	35	12.5		
5.04	35	12		
10	33	10		
40	34	6	—	Auricles beyond recovery; ventricle in perfect condition. Experiment ended.

B. Influence of Resorcin on the Bloodvessels.

EXPERIMENT XLI.—December 23, 1885. Terrapin 895 grms. Inflow canulas in right and left aortic trunks. Outflow canula in venous sinus. Arterial pressure 20 c.m. Venous pressure 0. Resorcinized saline contained 0.1 : 100 c.c.

Time P. M. From	to	Temp. Cent.	Total outflow.	Outflow per min.	Circulating fluids supplied to the vessels at the time mentioned on same line in second column.
3.26	—	—	—	—	Terrapin in box.
40	42	20°	24	12	
42	44	—	25	12.5	
44	46	—	24	12	
46	48	—	25	12.5	
48	50	—	26	13	On resorcinized saline.
50	52	—	18	9	
52	54	—	34	17	
54	56	—	50	25	On normal saline.
56	58	21	62	31	
58	4.00	—	52	26	
4.00	02	—	40	20	
02	04	—	40	20	
04	06	—	38	19	
06	08	—	41	20.5	
08	10	—	42	21	On resorcinized saline.
10	12	—	48	24	
12	14	—	70	35	On normal saline.
14	16	—	74	37	
16	18	21.6	62	31	
18	20	—	54	27	
20	22	—	54	27	
22	24	—	60	30	
24	26	—	54	27	
26	28	—	54	27	
28	30	—	54	27	On resorcinized saline.
30	32	—	68	34	
32	34	—	85	42.5	On normal saline.
34	36	—	88	44	
36	38	22	85	42.5	
38	40	—	76	38	
40	42	—	65	32 5	
42	44	—	62	31	
44	46	—	60	30	

Time P.M. From	to	Temp. Cent.	Total outflow.	Outflow per min.	Circulating fluids supplied to the vessels at the time mentioned on same line in second column.
4.46	4.48	—	60	30	
48	50	—	64	32	
50	52	—	62	31	
52	54	—	64	32	
54	56	—	65	32.5	
56	58	—	66	33	
58	5.00	—	66	33	
5.00	02	22.6°	65	32.5	
02	04	—	65	32.5	On normal saline.
04	06	—	70	35	
06	08	—	88	44	On resorcinized saline.
08	10	—	85	42.5	
10	12	—	80	40	
12	14	—	75	37.5	
14	16	—	68	34	
16	18	23	65	32.5	Experiment ended.

EXPERIMENT LIII.—January 6, 1886. Frog 86 grms. Curarized; tongue observed under microscope magnifying 60 diameters. Measurements of vessels made from camera drawings, stated in μ.

Time A.M.	Calibre of Art.	Cap.	Vein.	Remarks.
11.20	4.2	1 0	5	
25	4.2	1.0	5.2	
30	4.2	1.0	5.4	
35	4.2	1.0	5.2	5 drops of two per cent. solution of resorcin in saline applied to surface of tongue.
40	4.6	1.4	9.2	
45	5.2	1.6	10.8	Resorcin washed away with saline.
50	5.0	1.4	10.2	
55	5.0	1.0	9.8	
12.00	4.8	1.0	9.0	
05	4 0	1.0	9.0	
10	4.0	1.0	9.0	Surface of tongue very red, presenting the appearance of intense congestion.
15	3.6	1.0	8.6	
25	3.4	1.0	8.2	Experiment ended.

Experiment X. shows (1) that resorcin, in small doses, has no appreciable influence on either the rate of the heart or its work done; (2) larger doses reduce both rate and work; (3) still larger doses produce diastolic arrest; (4) atropin antagonizes its action to a certain extent only; (5) the sinus and auricles are much more quickly affected than the ventricle.

Previous experiments with resorcin on the heart having quite sufficiently demonstrated its strongly paralyzing influence upon sinus and auricles, very low venous pressure was used throughout Experiment XIX. In this manner any possibility of their being overworked was eliminated, and the fact that they were really in an excellent condition and capable of doing twice the amount of work which they were actually performing is shown in the observation taken at 4.25 P. M., at which

time, the venous pressure having previously been raised, the amount of work done was greatly increased.

Notwithstanding this, the veins, sinus, and auricles were promptly paralyzed by moderately large doses of resorcin, and lowering of the venous pressure had henceforth no effect on their condition, and, of course, raising it caused only a passive overdistention.

The ventricle, throughout this experiment and the three others on the terrapin with resorcin, showed a rather remarkable resistance to the influence of this drug, and the only effect it produced was a slight weakening and a considerable reduction in the rate of contraction. Very large doses, however, give rise to temporary diastolic arrest of the heart in the terrapin as well as in the frog.

The rather remarkable and quite unusual effect of resorcin on the rate of the heart's contractions, as shown in this experiment, is the result of the low venous pressure which was used.

From these and other experiments with resorcin on the heart, the conclusions are as follows: (1) Resorcin, in small doses, improves the heart's action; (2) In doses of medium size it paralyzes the sinus and auricles, but has little effect on the ventricle; (3) In very large doses it at once causes diastolic cardiac arrest, the ventricle recovering sooner or later, the auricles rarely ever.

Experiment XLI. on the bloodvessels shows that resorcin causes first contraction, then dilatation of the arterioles and capillaries.

Experiment LIII. shows—(1) That resorcin slightly dilates the arterioles, their dilatation being followed by contraction beyond the normal; (2) That it causes dilatation of the capillaries; (3) That it promptly and largely dilates the small veins, their dilatation far outlasting that produced in the arterioles and capillaries.

A consideration of the results of these experiments leads to the conclusion that resorcin reduces the temperature by increasing heat radiation by the dilatation it produces in the capillaries and veins, especially the latter.

The same quite remarkable preference for the venous side of the heart and vascular system is shown by resorcin in nearly the same degree as by thallin and hydrochinon. Resorcin paralyzes the auricles in doses which seem to improve rather than impair the contracting power of the ventricle, and it largely dilates the veins, while the arterioles are affected but very slightly.

As is the case with kairin, thallin, and hydrochinon, resorcin reduces the rate of beat of the heart probably by a stimulating influence on the terminal filaments of the pneumogastric, and dilates the vessels through a similar influence on the ganglia of the vasodilators. The tonic effect which it has upon the ventricle is most probably due to its direct action upon the muscular substance of the heart. We have, so

far, no explanation of the difference in the action of these drugs upon the two sides of the heart and vascular system. Nevertheless, the fact remains that all of the drugs so far considered possess this property nearly to the same extent. The only difference regarding their influence upon the heart lies in the ventricle. Kairin and thallin, in small doses, exercise but a *temporary* tonic influence over its contraction hydrochinon and resorcin a more *permanent* one. They all quickly paralyze the auricles and lower the tone of the walls of the veins. The natural consequence is that a much greater quantity of blood will be contained in the veins than in the arteries, and its passage from the veins back into the ventricle is greatly impeded, owing to the paralyzed condition of the auricles. Collapse, therefore, ensues; not so much from failure of the action of the ventricle, as from the danger of *bleeding the animal to death into its own veins*, to use the words of Ludwig.

V. Antipyrin.

Bettelheim (*Med. Jahrb. k. k. Ges. d. Aerzte*, Hefte ii. and iii., 1885) found that the injection of antipyrin caused a rise in the temperature over the integument and a fall in the rectum. This rise in the temperature of the integument was accompanied by a fall in the arterial pressure, and lasted for some time after the pressure began to rise; he was, therefore, led to conclude that the reduction in temperature following the administration of antipyrin is due to its causing a dilatation of the peripheral vessels and a contraction of the vessels of the viscera; hence, more blood being carried to the periphery, heat radiation is considerably increased. Bettelheim did not not notice any deleterious action of antipyrin on the heart. Queirolo (*loc. cit.*) also found that it produced a dilatation of the cutaneous bloodvessels, and that this condition of the vessels generally precedes the fall in temperature.

According to Cappola, the action characteristic of antipyrin is that it produces a fall in the temperature, normal or pathological. This apyrexia, he thinks, does not depend upon its retarding the processes of combustion within the organism, for antipyrin has no such influence; nor does it depend upon cardiac depression, for the contractions of the heart are much increased in force, and the blood-pressure is not lowered. In his opinion, which is based upon experiments upon the vessels of the lungs of the frog and the dog, antipyrin produces its characteristic effect by dilating the bloodvessels, and in doing this it facilitates the radiation of heat. This dilatation is, furthermore, said to be independent of the vasomotor contres, for it takes place in the vessels of isolated organs, and is therefore due to a direct action of antipyrin upon the blood-vascular walls, probably to stimulation of the vasodilator nerve ganglia. In order to induce poisoning by this drug, it requires doses which are far greater than those which are necessary for the production of apyrexia.

Death takes place by arrest of respiration. Even when administered in toxic doses, Cappola found that the blood-pressure did not diminish, and the heart continued to beat with great energy, and was finally arrested in systole (*Arch. It. de Biol.*, 1884, fasc. ii. 134). Filehne found the heart after death arrested in diastole, and also Arduin states that antipyrin kills by heart paralysis.

In therapeutical literature we find two cases of collapse reported as occurring after the use of antipyrin in typhoid fever patients. But, with the exception of these two cases, not one of the newly discovered remedies of the class of antipyretics is so favorably spoken of and so generally recommended as is antipyrin. All clinicians, after thoroughly and extensively experimenting with this remedy, agree that it is absolutely safe, and reduces the temperature promptly, and without causing any of the bad symptoms characteristic of the administration of kairin, thallin, etc. The perspiration which sometimes occurs is a relief for the patients, and not at all unpleasant.

Guttmann (*Berl. klin. Woch.*, 1885, xxii. 377, 401) pronounces antipyrin the safest and most powerful of all antipyretics, and Lehmann attributes to it all the good qualities of a perfect antipyretic.

My experiments with this drug are confirmatory of the many good qualities possessed by antipyrin.

A. Influence of Antipyrin on the Heart.

EXPERIMENT XXX.—December 7, 1885. Frog 195 grms. Sheep's blood and Ringer's saline (1 : 1½). Inflow canula in inferior vena cava. Outflow canula in two aortic trunks. Venous pressure 3 c.m. Arterial pressure 10 c.m. Antipyrinized blood contains 1 grm. in 100 c.c. of normal blood mixture.

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in the first column.
3.20	—	—	—	Frog in box.
40	29	10	15.4°	
45	29	10		
50	29	10		
55	29	10		
4.00	29	10		
05	29	10		
10	29	9.5	15.8	
15	30	9.5		
20	30	9.5	—	On antipyrinized blood.
22	29	10		
24	27	10		
26	26	10.5	—	Auricular contractions much more thorough than under normal blood; ventricular systole more complete and considerably prolonged.
30	25	10.5		
35	23	10		
40	21	10	—	On normal blood mixture.
45	24	9	15.2	
50	24	9		
55	24	9		
5.00	24	8.5	—	On antipyrinized blood.
03	21	7		
06	20	7		

Time P. M.	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in the first column.
5.09	19	7		
12	19	7		
15	18	6.5	—	Entire heart much smaller than under normal blood; auricles contracting completely; ventricle same, looks whitish during systole.
20	18	6.5		
25	17	6.5		
30	16	6.2	—	On normal blood.
35	19	7		
40	20	7		
50	21	7	—	Venous pressure raised 2 c m.
55	25	10		
6 00	28	12	—	Heart in perfect working order.
05	28	12		
10	28	12.5	—	Experiment discontinued.

EXPERIMENT XVIII.—November 19, 1885. Terrapin 1120 grms. Beef's blood and Ringer's saline (1 : 1½). Inflow canula in inferior vena cava. Outflow canulas in right and left aortæ. Venous pressure 7 c.m. Arterial pressure 22 c.m. Antipyrinized blood in different degrees of strength was used.

Time P. M	Rate per min.	Work in c.c. per min.	Temp. Cent.	The circulating fluids were supplied to the heart at the time mentioned on the same line in the first column.
3.10	—	—	—	Terrapin in box.
3.50	31	29	22°	
55	31	28		
4.00	31	29		
05	32	30		
08	32	30		
16	32	30	—	On antipyrinized blood (1 grm : 500 c.c.).
18	32	40		
21	32	41		
24	32	41		
27	32	41	—	Through 500 c.c. of antipyrinized blood; on normal blood.
29	33	31	22.5	
35	33	26		
40	33	25		
45	32	25	—	On antipyrinized blood (2 grms. : 500 c.c.).
47	33	30		
52	32	40		
55	32	40		
58	32	40		
5.00	32	32	—	Through 500 c.c. of antipyrinized blood; on normal blood.
04	33	27		
07	33	26		
10	33	25	—	On antipyrinized blood (4 grms. : 500).
12	33	30		
15	32	35		
18	31	32	22	
20	30	29		
22	30	25		
25	29	25	—	Through 500 c.c. of antipyrinized blood;
27	30	26		on normal blood.
29	30	30		
31	31	30		
33	31	26		
40	33	25	—	Experiment ended.

B. *Influence of Antipyrin on the Bloodvessels.*

EXPERIMENT XXIV.—December 5, 1885. Terrapin 870 grms. Inflow canulas in right and left aortæ. Outflow canula in sinus. Arterial pressure 12 c.m. Venous pressure 0. Antipyrinized saline contained 1 grm. of antipyrin to 100 c.c. of Ringer's saline.

Time P.M. From	to	Temp. Cent.	Total outflow.	Outflow per min.	
2.15	2.45	26.6°	—	—	Terrapin in box.
45	47	27.2	12	6	
47	49	—	11.5	5.7	
49	51	—	12	6	
51	53	—	12	6	
53	55	—	13	6.5	
55	57	—	13	6.5	
57	59	—	13	6.5	
59	3.01	—	13	6.5	On antipyrinized saline.
3.01	03	28	13	6.5	
03	05	—	19	9.5	
05	07	—	35	17.5	
07	09	—	46	23	Off antipyrinized saline.
09	11	—	50	25	
11	13	—	50	25	
13	15	—	48	24	
15	17	—	42	21	
17	19	—	40	20	
19	21	—	37	18.5	
21	23	—	30	15	
23	25	—	28	14	
25	27	—	28	14	
27	29	28.4	28	14	
29	31	—	28	14	On antipyrinized saline.
31	33	—	28	14	
33	35	—	35	17.5	
35	37	—	40	20	
37	39	—	48	24	Off antipyrinized saline.
39	41	—	50	25	
41	43	—	48	24	
43	45	—	44	22	
45	47	—	42	21	
47	49	—	38	19	
49	51	—	37	18.5	
51	53	29	36	18	
53	55	28.2	34	17	
55	57	—	30	15	
57	59	—	30	15	
59	4.01	—	29	14.5	
4.01	03	—	26	13	
03	05	—	25	12.5	
05	07	—	25	12.5	On antipyrinized saline.
07	09	—	28	14	
09	11	—	32	16	
11	13	—	37	18.5	
13	15	—	44	22	
15	17	—	35	17.5	Off antipyrinized saline.
17	19	—	34	17	
19	22	—	47	15.6	
22	24	—	29	14.5	
24	26	—	26	13	
26	28	—	25	12.5	
28	30	—	24	12	
30	32	—	24	12	
32	34	—	25	12.5	Experiment ended.

EXPERIMENT LVI.—January 7, 1886. Frog 94 grms.; curarized. Tongue observed under microscope magnifying 60 diameters. Measurements of vessels made from camera drawings, and stated in μ.

Time P. M.	Art.	Calibre of Cap.	Vein.	Remarks.
2.35	5.4	1.0	6.2	
37	5.4	1.0	6.4	
40	5.4	1.0	6.4	Injected 0.05 grm. antipyrin into lymph-sac.
42	5.2	1.0	7.0	
44	4.8	1.0	7.0	
47	5.0	1.5	7.2	
50	5.2	1.4	7.4	
53	5.2	1.4	7.4	Applied to surface of tongue solution of 1:500.
56	5.2	2.0	7.4	
4.00	5.2	2.0	8.0	
05	5.0	2.0	8.0	Applied solution of 1:100
10	5.0	2.0	8.6	
14	5.0	2.6	9.6	
19	5.4	2.6	9.8	
24	5.4	2.8	10.6	Current in veins much slowed; arteries still very active; no flow in some capillaries.
27	5.4	2.8	12.4	
30	6.0	2.8	13.2	
40	6.2	2 8	14.2	Experiment ended.

At the end of this experiment, the current in all superficial capillaries and veins was entirely arrested, due to a coagulation of the blood within their walls. There was a rich, thick plexus of the capillaries not noticed at the beginning. The deeper veins and capillaries, as also the arterioles, were still pervious, and a brisk current was running through them.

Experiment XXX. shows that it requires enormous doses of antipyrin to reduce appreciably the amount of work done by the heart of the frog, otherwise so sensitive; the rate is reduced much more quickly than the work done; the muscular structure remains unaffected, and the force of the cardiac contractions is rather intensified than diminished.

Experiment XVIII. shows that smaller doses than were used in the previous experiment increase the work done 25 per cent. and have no influence at all on the rate. Even a dose of 2 grammes of the drug passed through the heart within fifteen minutes increases the work without reducing the rate; it required 4 grammes of antipyrin to bring about an appreciable decrease in the rate and the work done. At the end of both these experiments the energy of the hearts under observation left nothing to be desired, notwithstanding the fact that their own weight of the drug had been passed through them several times during that period.

The same must be said in regard to the bloodvessels of the terrapin; for it was found that a 1 per cent. solution of the drug in Ringer's saline was required to produce dilatation of the arterioles.

Experiment LVI. shows that antipyrin, in very small doses, injected

into the lymph-sac of the frog very slightly contracts the arteries, but dilates the capillaries and veins; in large doses, applied directly to the surface of the tongue, it gives rise to extensive dilatation in the veins and also the capillaries; a 1 per cent. solution of it applied to the tongue of the frog will, after a short time, cause coagulation in all the superficial bloodvessels.

The manner in which antipyrin reduces temperature is purely by increasing heat radiation, owing to its extensively dilating the veins and capillaries; but what stamps it as an excellent antipyretic is that, besides dilating the veins, it also has a tonic influence on the heart and slightly increases arterial pressure, or at any rate does not cause a diminution of the same. It has, moreover, no injurious influence on the blood or the muscular tissues, and strengthens the auricles.

The objection to the employment of kairin and thallin as antipyretics is from the fact that they cause heart paralysis, especially affecting the auricles, in doses only slightly larger than are sufficient to produce a lowering of the temperature. But this objection becomes an absolute danger when we take into account the destructive influence upon the blood corpuscles and tissues generally.

Hydrochinon and resorcin, although not exerting the same weakening and directly paralyzing influence upon the ventricle of the heart which is peculiar to kairin and thallin, both paralyze the venous side of the heart, viz., the auricles, and greatly lower the tone of the walls of the veins. The extra amount of blood, therefore, which is driven into the veins through the increased action of the ventricle, is only with great difficulty returned to the ventricle, and here the danger is not so much from failure in the power of the ventricle as in the case of kairin and thallin, as from the danger of *bleeding the animal to death into its own veins*. The intense visceral and especially pulmonary congestion found on post-mortem, by Dujardin-Beaumetz, and others, in animals killed by resorcin, seems to confirm this view of the matter.

Antipyrin, though largely dilating the veins, increases the power of contraction of both auricles and ventricle, and has no injurious influence upon the blood nor the muscular tissues, and therefore possesses, indeed, all the good qualities of a perfect antipyretic.

LABORATORY OF THE MUSEUM OF HYGIENE,
WASHINGTON, D. C.