Fever : its pathology and treatment by antipyretics : being an essay which was awarded the Boylston prize of Harvard University, July, 1890 / by Hobart Amory Hare.

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FEVER:

ITS PATHOLOGY AND TREATMENT BY ANTIPYRETICS.

BEING AN ESSAY WHICH WAS AWARDED THE BOYLSTON PRIZE OF HARVARD UNIVERSITY, JULY, 1890.

BY

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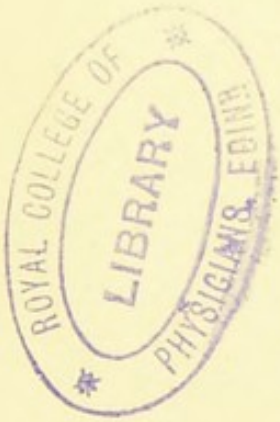

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THIS ESSAY IS DEDICATED

BY THE AUTHOR TO

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AS AN EVIDENCE OF

VERY WARM REGARD.

PREFACE.

It would be difficult to find any theme about which so much has been written in the past ten years as the subject with which this essay deals, and a concise summary of the conclusions of many of the best observers cannot fail to be of value to the busy practitioner, particularly when combined with sufficient experimental and clinical experience to make the work something more than a mere compilation of other people's ideas. Not the least important portion of the book is the record of untoward effects produced by the various drugs considered, and it is interesting to note how severe the symptoms often seemed to be, and yet how few of the patients so affected died.

The following is extracted from the minutes of the Boylston Prize Committee:—

By an order adopted in 1826, the Secretary was directed to publish annually the following votes:—

1. That the Board do not consider themselves as approving the doctrines contained in any of the dissertations to which premiums may be adjudged.

2. That in case of the publication of a successful dissertation the author be considered as bound to print the above vote in connection therewith.

The title of this essay, when presented to the Boylston Prize Committee, early in 1890, was, "The Uses and Values of Antipyretics."

FEVER:

ITS PATHOLOGY AND TREATMENT.

INTRODUCTION.

THE interest and importance which is very properly attached to the use of certain drugs in the treatment of pyrexia in man has already led to the production of a large number of researches on this subject, some of which have been exceedingly valuable from more than one point of view, and, curiously enough, that country which is at once the youngest and most pushing for money, and not science, has been the source from which many of our reliable and accurate studies have come. The readers of this essay are too well grounded in the study of the condition known as fever to make it necessary for me to detail the studies so far made. Suffice it to state that the medical profession are almost universally of the opinion that fever is a disorder of calorification depending upon nervous action, said nervous action being the result of various causes, such as the presence of poisonous materials in the blood, or of perverted functional activity. The first of these may be represented by the fever of any infectious disease, the second by the so-called hysterical hyperpyrexia.

Turning from the general question of fever to those drugs which combat it, we are met at once by an array of synthetically prepared substances which are almost without number, and which are derived chiefly from the tar found always in close proximity to deposits

of coal. Though the title of this essay is a sweeping one, it is hardly to be supposed that all these drugs must be included; only the more important members of the antipyretic group are therefore studied, such as antipyrin, antifebrin, phenacetin, thallin, and salicylic acid.

The value of a drug which can decrease high temperature by influencing heat production alone cannot be overestimated, and, while several of the drugs named seem to influence this part of the heat apparatus more than that portion connected with the dissipation of heat, we have no substance which is distinctly and solely capable of exercising an inhibitory power over the development of heat in the body.

Frequently, one of the substances put forward by its discoverer as a useful antipyretic has been found to so depress the heart or the respiration that it cannot be used, while another produces secondary lesions in the tissues of the body by a more slowly acting influence.

For both experimental and practical purposes we may, therefore, divide antipyretics into three great classes, as follows:—

First.—The substances which allay or prevent fever by inhibiting its production.

Second.—The drugs which possess the power of decreasing the production and increasing the dissipation of heat.

Third.—The compounds which allay fever, not by stopping the manufacture of heat-units, but by so increasing the radiation of heat that the loss is greater than the manufacture.

The first and third classes are directly opposed to each other. The second class is half-way between, and it is to this class that most of our antipyretic drugs

belong. The first class is the ideal; the second is the one we have to be content with; the third is that used by our forefathers, and is the most unreliable and harmful, since the tissues are quite as rapidly destroyed under their influence as they were before the drug was given; the centre of the body remaining in pyrexia, while the cool skin and extremities are apt to lead the physician into the belief that the fever no longer exists. The tissue-waste of the fever goes on unchanged, and the patient, if the disease be prolonged or asthenic in character, is in almost as serious a condition as if no attempt to reduce his temperature had been made. It should never be forgotten that hyperpyrexia, or even an ordinary fever, is dangerous in two ways, namely, by destroying tissue, and thereby reducing vital power, or by acting simply as too great bodily heat, and thereby producing nervous or cardiac symptoms, such as are seen in cases of sun-stroke and heat exhaustion, in which the condition of the patient is the result of coagulation of the cerebral or cardiac protoplasm, or is one of depression of all vital function.

Closely allied to this question is that which asks us to define what we mean by hyperpyrexia. As given in most works on fever, this term is applied to any state in which the temperature reaches 106° or 107° F.; but in reality the figures have nothing to do, except in an indirect way, with what the student or physician wishes to know. A temperature of 106° F., in a young, healthy man suffering from an acute attack of some short-lived disease, does not mean very great danger; but a temperature of 103°, day after day in typhoid fever, does mean danger, and must be carefully attended to. In simple, continued fever, 106° F. is a hyperpyrexia; in typhoid, or other low fever, 103° F. is a hyperpyrexia. The

question is not one of actual degrees Fahrenheit, but rather as to whether the temperature present is doing any harm.

Returning to the drugs which can be divided into classes according to their physiological effects, we may classify them as follows:—

1. Those which decrease heat production alone are not known.

2. Those which act both on dissipation and production are antipyrin, antifebrin, carbolic acid, salicylic acid, similar substances, and quinine.[1]

3. Those which only dissipate heat, as far as we know, namely, the great group of cardiac sedatives and their allies, such as aconite and antimony.

No one is more sensible than the writer that this arrangement of the subject is partly artificial. In the study of these drugs, both experimentally and clinically, two facts are present which are exceedingly confusing and almost impossible to separate. Given a drug which decreases fever, we find that do what we will we cannot invent any accurate apparatus which will determine whether the decrease in heat dissipation, which accompanies the decrease in production, is the result of that decrease in the manufacture of heat, or is due to a direct action of the drug upon the function of dissipation itself. If we throw water on a fire we know that the heat production is decreased, and that the giving off of heat must also be decreased; but if the fire and stove be heavily coated with clay we have a state in which both the production of heat and the dissipation are directly interfered with. In the first instance dissipation is decreased secondarily or indirectly.

[1] In this class also should be placed cold bathing, which probably decreases heat production as well as increases dissipation.

In the second instance dissipation is affected primarily and directly. As the relation between these two great governing factors in the balancing of bodily temperature is difficult of understanding, they may be tabulated to make them clear.

Bodily temperature may be raised by—

(*a*) Increased production of heat.

(*b*) Decreased dissipation of heat.

(*c*) Increased production and increased dissipation, the dissipation not keeping pace with production.

(*d*) Normal production associated with decreased dissipation.

In any of these instances the temperature of the body rises because the heat is made faster than it can be dissipated from the surface. On the other hand—

Bodily heat may be decreased by—

(*a*) Decreased production of heat.

(*b*) Increased dissipation of heat.

(*c*) Increased production and increased dissipation; when the second factor is more active than the first.

(*d*) Normal production, with excessive dissipation.

The actions of most of the drugs which exercise an antipyretic influence have been studied upon animals, and, although the practical use of all drugs must depend on the results obtained by the clinician, much may be done by careful researches in the physiological laboratory which discover serious contra-indications and dangers. The experimental and clinical side of medicine should be studied hand in hand, the first saving the practitioner from error and giving him a foundation on which to base his actions, and the second showing him by experience the minor details which it is so necessary for him to understand.

A discussion of the methods resorted to by various

experimenters upon fever is not in place here. Suffice it to say that some of the most laborious researches have been carried out by skilled investigators, only to arrive at the most contradictory conclusions. Thus, in a very recent essay, showing a vast amount of labor, Winternitz, assisted by Paschkis and Pal,[1] has given us the results reached by using thermometers applied inside of air-tight boxes to the skin, the bulbs of the instruments being flattened so as to offer a greater surface. By this means the production and dissipation of heat were measured (?). Any one who has studied fever knows that in certain diseases, though the skin may be cold and clammy, the central temperature may be exceedingly high; and it is also a well-known fact that the heat given off by the skin varies with every flush of blood which goes to and leaves the surface.

Some years since, Beyer[2] attempted to show, by experiments made with certain antipyretics upon the blood-vessels of the terrapin, that these drugs lowered fever by increasing heat dissipation alone, because he found that the blood-vessels of the terrapin were dilated by these drugs. From such a study this careful observer enunciates in italics "that antipyrin lowers temperature by this means." It is such statements that give rise to the contradictory turmoil which is continually going on. The only accurate method that we can resort to is one which will account with mathematical exactitude for every unit of heat made or lost. There are two calorimeters, so called, which will do this with more or less accuracy.

The first of these is that of d'Arsonval, which simply consists of one cylinder within another, the space be-

[1] Zur Pathol. und Hydrotherapie des Fiebers. Leipsic, 1888.
[2] Amer. Jour. Med. Sciences, April, 1886.

tween being filled with water. An air-tube enters the inner compartment to give air to its occupant, and then passes into the water in the form of a coil, in order to give any heat in the air expired by the animal in the inner box to the water before the air escapes into the surrounding atmosphere.

This calorimeter is inaccurate, in that it does not prevent the escape of heat from the water, owing to the outer cylinder being uncovered.

The other calorimeter, which was used by Wood in his early studies, is also open to many errors. Arranged, as is the d'Arsonval, so far as the passage of the air through the box and water is concerned, yet more accurate, in that the outer cylinder or box is protected from the atmosphere by hair-packing and a wooden cover, it nevertheless is faulty because every time the animal is taken out of the box this receptacle must be lifted bodily out of its envelope of water, all the air-pipes disconnected and the thermometers removed, and an air- and water- tight door unscrewed. All these changes take time and expose the water in the outer box to the atmosphere, while the dripping sides of the inner box, by the evaporation of the water, cool it by several degrees, so that when it is returned to its casing of liquid it in turn lowers the temperature of the water in the tank. Further, if the door be not most carefully applied, water leaks into the animal compartment, and the experiment is either ruined by the drowning of the dog or the chilling of his body.

These objections, however, no longer exist, having been recognized by Dr. Wood and obviated chiefly through the ingenuity of Dr. Reichert.

The Pulse in its Relation to Fever.—For many years the profession of medicine have been in the habit

of "feeling the pulse" with the perfectly proper object of determining what the state of the system is, as it appears on this sign-board of the body; but it has only been of late, when our knowledge has supposably increased, that we have come to consider the pulse-rate and force as anything more than a simple aid. At present, many seem to forget that the very value of the pulse as a sign-board depends on its readiness to obey the beck and call of the variations in the system, and to consider that in fever, for example, the pulse is rapid not because the fever makes a rapid pulse, but that a rapid pulse and fever are equally important conditions.

In other words, these persons regard the rapid pulse not as the result of the heightened temperature, but as a symptom of itself.

While in our present state of knowledge concerning the poisons which produce fever we cannot assert that none of them act on the heart in the same manner as does a drug, thus altering the pulse-rate and force, we are able by experimentation to prove that high temperatures, of themselves, do alter the heart-beat, and, in addition, that antipyretics, as a general rule, in lowering the fever lower the pulse, not directly, but indirectly. Such results are to be gleaned from the studies of Lauder Brunton and Newell Martin, as well as several other workers in this field, who have proved that febrile temperatures stimulate the accelerator cardiac nerves.

Closely associated with this question is that of the relationship between arterial pressure and fever.

It at once becomes evident that if heat stimulates the accelerator nerves an increased rapidity of cardiac action must ensue, and in consequence an increase in the amount of blood thrown into the arteries must result; also that as a consequence of these changes the

arterial pressure must rise, even if the vasomotor system itself responds in no way to the action of the heat. In nearly all cases of high fever, unless the system be greatly exhausted, the vasomotor apparatus certainly is excited to increased activity.

The Dangers of Fever.—As the dangers of high fever have already been spoken of, the impression ought not to be given that every one believes, with Liebermeister, in the absolute harmfulness of such states. While most of the profession have accepted such views, their opponents, while not in large number, have been so prominent as individuals that their studies cannot be passed by. In 1883 Unverreicht[1] tried to rebut the testimony then so rapidly accumulating in favor of antipyretic measures, and still later Naunyn,[2] in a very carefully written and logical paper, has strongly denied their value and usefulness. While he grants that high temperatures are most important for prognosis and diagnosis, and that certain antipyretic measures do good, he nevertheless insists that a raised temperature is an index, not a cause, of evil, and that the cold bath does good primarily by its effects on the nervous system, not by its direct action on the fever. He acknowledges, of course, that such temperatures as 108° to 110° F. are of dangerous import in themselves.

The question of the relative action of high fever on the body and that of antipyretics is sufficiently important to require some thought. To prove that his assertions are correct, Naunyn gives the results reached in a series of studies made by him on men and animals. He found that healthy rabbits will bear an artificially induced temperature of 106° to 107° F., rising at times

[1] Deutsche Med. Wochenschrift, 1883, S. 67.

[2] Archiv für Experimental Path. und Pharmacol., 18, 2 S., pp. 48–124.

to 108° or 109° F., for days together without any injury, if plenty of air and drink be given them; and he was unable, on making autopsies, to find any lesions present as a result of the experiment, except a slight cloudiness of the renal epithelium.

It is worth while to call attention to two facts which have been apparently overlooked by Naunyn and many of the readers of his paper, namely, that 106° to 107° F. are only a few degrees above the rabbit's normal heat, which is about 103° F.; so that the pyretic temperature of these animals corresponded to but 101° to 102° F. in man,—a temperature easily borne in many fevers. Secondly, it should be remembered that in these studies heat was constantly applied to maintain the abnormal temperature, and the animal did not manufacture the heat itself. Although at first sight this seems unimportant, it ought not to be overlooked. The tissue changes in the two instances are entirely different. To use a humble simile: in the one case the stove is kept hot by heat applied to its exterior without any combustion of the coal (its tissues) inside of it; in the other case the heat is maintained by the use of the coal itself. Very different changes are naturally found in the coal in the two cases. Much more might be said of this, but the entire subject may be summed up as follows, viz., that while high temperatures are borne in some instances with no evil result, the majority of cases do not turn out so favorably.

ANTIPYRIN.

Experimental Evidence.

No sooner was this drug placed before the profession than numerous trials of its powers were made in the laboratory, as well as at the bedside; so that at the present time we have a mass of material in the form of reports which is stupendous.

Heat Functions.—In studying the influence of any drug upon bodily heat, the first point which arises before us is, whether or not it lowers normal bodily temperature. The evidence in regard to this point is somewhat contradictory, yet it is possible to bring order out of the chaos. As early as the winter of 1885–1886, Wood, Reichert, and the writer[1] carried out a series of experiments upon this subject. We found that, in the animal in which no febrile movement was taking place, antipyrin caused a fall of temperature amounting to several degrees Fahrenheit.

These results have been confirmed by those of Pavlinow[2] and Anserow,[3] the first of whom noted a fall in the temperature in normal animals amounting to from 1° to 2° C. Anserow, using animals free to run about, reached results of similar import, in so far as the rectal temperature was concerned, although he asserts that the surface temperature was raised. The doses of these two investigators were, however, enormous,—from 30 to 100 grains. Umbach[4] has noted a fall in his own normal

[1] Therapeutic Gazette, September, 1886.
[2] Meditzenskoie Obozrenie, fasc. xii, 1885, p. 1203.
[3] Congress of Russian Medicine. Moscow, 1887.
[4] Arch. für Experiment. Path. und Pharm., xxi.

temperature, amounting to 1.4° C., after having taken 60 grains twice in two days, and this is confirmed by Jacubowitsch,[1] who found that a fall of temperature occurred in healthy children under the influence of antipyrin.

Although, at first glance, it would appear from these foreign observers, and indeed from the results reached in this country, that a very considerable fall takes place, there are, nevertheless, several points which close examination of these papers brings forth. In the first place, a very serious element of fallacy attaches itself to experiments made upon animals *tied down* upon tables, or animal-holders, simply because such animals lose their bodily heat very rapidly under such circumstances.

This element of fallacy is present in the studies of Wood, Reichert, and the writer, and Pavlinow.

The following experiments emphasize this fact, and all physiologists recognize that such changes do occur :—

Experiment No. 1.—Dog; weight, 22¼ lbs. Full grown. Dog tied in a dog-trough such as is used in laboratories.

11.45.	Rectal temperature,	. . . . .	102.4
11.50.	"	"	102.4
12.	"	"	102.3
12.10.	"	"	102.1
12.20.	"	"	101.7
12.30.	"	"	101.8
12.40.	"	"	101.2
12.50.	"	"	101.
1.20.	"	"	100.3

Experiment No. 2.—Dog; weight, 32 lbs. Full grown. Tied on table :-

[1] Jahrbuch für Kinderheil., 1885, Bd. xxiii, No. 4.

10.15.	Rectal temperature, ...	103.2
10.25.	" "	103.1
10.35.	" "	103.1
10.45.	" "	103.
10.55.	" "	102.2
11.	" "	101.9
11.10.	" "	101.7
11.20.	" "	101.7

Again, in the experiments of Pavlinow, Anserow, and Umbach, the amount of the drug given was almost toxic, and the result cannot be considered as an effect of a medicinal dose. That toxic doses are capable of *greatly* lowering temperature is not only a very likely hypothesis, but an established fact. Aside from clinical observations made in cases of poisoning, we have the experiments of Bouchard,[1] Henocque,[2] Arduin,[3] and Huchard,[4] all of whom have found that large quantities of antipyrin may cause a fall of as much as 6.2° C.

In order to determine whether all the fall which occurred was due to the antipyrin or to the constrained position of the animal, the writer made two experiments on free animals to determine this point, using a somewhat smaller dose. A slight fall occurred, which did not exceed more than one degree.

Experiment No. 3.—Dog; weight, 20 lbs. Full grown. Free to run about room.

12.05.	Rectal temperature, ...	103.2
12.06.	Gave 4 grains of antipyrin into jugular vein.	
12.10.	Rectal temperature, ...	103.1
12.15.	" "	103.0
12.20.	" "	102.8
12.30.	" "	102.7
12.40.	" "	102.2

[1] Comptes Rendus de Soc. Biologie, No. 43.
[2] Gazette Hebdomadaire. [3] Thèse de Paris, 1885.
[4] Société de Thérapeutique. Bulletin, 1885.

12.50.	Rectal temperature	102.3
1.00.	" "	102.2
1.10.	" "	102.1
1.20.	" "	102.1
1.30.	" "	102.0
1.40.	" "	102.3
1.50.	" "	102.3
2.00.	" "	102.3

Experiment No. 4.—Dog; weight, 18½ lbs. Full-grown. Free to run about.

2.10.	Rectal temperature, ...	103.8
2.12.	Gave 4 grains antipyrin by jugular vein.	
2.20.	Rectal temperature, ...	103.7
2.30.	" "	103.2
2.40.	" "	103.1
2.50.	" "	103.0
3.00.	" "	102.8

It should also be remembered that in the calorimetrical studies of Wood, Reichert, and the writer on normal animals a similar fall occurred, and, as these dogs were not tied down, the results are confirmatory of the conclusions already given.

There can be no doubt, therefore, that antipyrin in ordinary doses may lower the normal bodily temperature more or less completely, according to the amount given and the susceptibility of the recipient.

Calorimetrical Studies.—Owing to the expensiveness and cumbersomeness of the apparatus involved, very few investigators have attempted to study the effects of antipyrin by this means.

Three such studies have, however, been published, namely, that of Wood, Reichert, and the writer,[1] those of P. J. Martin[2] and those of Destree.[3] The last two investigators confined their experiments to fevered animals.

[1] Therapeutic Gazette, Sept., 1886. [2] Therapeutic Gazette, 1887.
[3] Journal de Médecine de Bruxelle, July 20, 1888.

In the calorimetrical studies made by the first of these investigators upon animals whose temperature was normal, it was found that the drug, as a general rule, caused a reduction in the temperature, and that the cause of this fall was dependent upon a decrease in the production and dissipation of animal heat. In seven out of nine studies this phenomenon was produced, but in the remaining two, though the bodily temperature fell slightly, yet the calorimeter showed an increase in heat production and dissipation instead of a decrease, as in the others. These two results we ascribed to the fact that large doses of antipyrin have been found to be productive of a rise in bodily heat associated with convulsions; but this explanation is not a satisfactory one, for, according to our own studies, a much larger dose is needed to cause convulsions than that which we gave to produce these variations in body-heat. Further than this, the record of the rectal temperature in these cases fails to show that an increase in bodily heat occurred. Some other cause for these results must, therefore, exist than those of which we speak.

The fact that seven of our nine experiments were similar in result shows, however, that the conclusions as to the mode of fall may be considered as correct, and it is probably true that heat production is primarily lessened and followed by a decrease in heat dissipation.

There are several facts in relation to some of these experiments which must be carefully examined into, chief among which is the degree of fall in temperature following the ingestion of the drug. As has already been pointed out in the early part of this paper, the variation in the bodily heat of a dog is so great that a change of a fraction of a degree in temperature ought not to be regarded as the result of the action of a drug, although

it may point toward the general result if the same phenomena frequently present themselves. Thus, in Experiment No. 65 of our series the dog's temperature fell 2.1° F. before the drug was used, and only 1.0° F. after it was given; so that, while the total fall of temperature was from 104.4° F. to 101.5° F., more than two-thirds of this drop was independent of any effect of the drug.

This same state of affairs, to a less degree, holds good in several of the remaining experiments which are detailed.

Not only do the clinical cases of every one prove that antipyrin decreases fever, but in addition the studies of Wood, Reichert, and the writer, and those of Martin show us that this is the case. Still further confirmation is to be found in the experiments of Girard,[1] who, puncturing, as did Martin, the corpora striata, found that antipyrin caused a decrease in the resutling high temperature. To give a long list of clinical authorities is, therefore, useless, and the writer will pass from the consideration of the influence of antipyrin upon the normal animal to that of its effect on the dogs suffering from fever, still examining and considering the studies of Wood, Reichert, and himself, as they are our chief leaders in this question. We concluded that antipyrin lowers fever by the same action as we believe it affects the normal temperature, namely, by a primary decrease in heat production, followed by a secondary decrease in heat dissipation. These conclusions have a better basis than their predecessors, and are probably correct. Further than this, they are confirmed by the studies of Martin,[2] carried out some time later, who finds that antipyrin decreases heat production, but increases heat

[1] Revue Méd. de la Suisse Romande, 1888.

[2] Therapeutic Gazette, 1887.

dissipation, a discrepancy in result which might well occur, in view of the secondary rôle played by heat dissipation under such circumstances. Still more recently Destree,[1] of Brussels, has reached conclusions identical with those of Wood, Reichert, and the writer, and differing in consequence from those of Martin in the particular named. As the last two observers used the calorimeter of d'Arsonval, these results may be considered as facts which rest on undeniable evidence, since the same results are reached by different men using different instruments and different methods of producing fever.

Though the much more accurate method of studying heat functions has permitted us to make these deductions, much has been said by various persons as to the effect of antipyrin upon the sweat-glands, and the possibility that the fall of temperature depends on the profuse sweat produced. That the profuse sweat is not responsible for the fall in temperature is proved by a very simple experiment which can be tried at any time, and which consists in the hypodermic injection of a dose of atropine previous to the administration of the antipyrin. Although the sweat does not appear, the temperature nevertheless falls.

Bettelheim[2] has attempted to determine the physiological action of antipyrin by a series of experiments in the laboratory of von Basch, which are prostituted by the hypothetical conclusions which he draws from them. He says: "It is intelligible that when—as follows from the elevation of the skin temperature—the skin vessels are dilated and the internal blood-vessels—as follows from the increased blood-pressure—are con-

[1] Journal de Méd. de Chir. et de Pharm., July 20, 1888.
[2] Med. Jahrb. d. K. K. Gesellsch. d. Aerzte in Wien, 1885.

tracted, a larger quantity of blood streams through the skin vessels in a unit of time, and there dissipates its heat, so that gradually the entire mass of the blood is cooled down."

This is such a pure hypothesis that no one can understand how any one could state it, for he states at one and the same time that the skin vessels are dilated by the same temperature that contracts the internal blood-vessels, and utterly ignores the fact that, as there is a mechanism for heat dissipation, so must there also be one for heat production. The experiments of Maragliano[1] with the plethysmograph of Mosso lead him to conclude that antipyrin dilates the dermal blood-vessels, and he also reaches the same conclusion as do Bettelheim and Murri,[2] and with no more ground for his statements asserts that the decrease in temperature is due solely to the increased heat dissipation. Beyer[3] has made equally unfortunate statements as a result of his studies on the vessels of the tortoise.

Circulation.—As has already been stated, the close association which exists between febrile processes and changes in the circulatory system makes their study of great interest when drugs are used to lower temperature.

Referring once more to the studies of Wood, Reichert, and the writer, we find a number of experiments bearing on these points. Beginning with the normal animal, we find that while here, as in the calorimetrical experiments, the bodily temperature fell in the normal dog after the use of antipyrin, the fall is not accompanied by any changes of moment in the circulatory system, as is shown when the animal is attached to the manometer and kymograph. In the first experiment detailed the tem-

[1] Gazz. degli. Osp., 1872–82.
[2] *Ibid.*, 1888–91.
[3] Amer. Jour. Med. Sci., April, 1887.

perature progressively fell without any circulatory change of moment. In the second the doses were so enormous that convulsions were produced almost at once, thus making the record practically useless; and in the third the dose was so large that, while at first the temperature fell without much change in the circulation, convulsions ultimately arose and disturbed the result.

The first record is the only one, therefore, which is perfectly clear, while the third confirms it, and this single instance would seem to show that there is no relationship between the fall of temperature and arterial pressure.

Whatever may be the cause of the changes in normal temperature, one thing seems certain, namely, that antipyrin does not directly influence in any way the circulation itself, either in fever or health, unless the dose is massive and toxic in effect. This seems proved, not only by the studies just quoted, but also by the researches of many others, although some evidence of importance points in an opposite direction.

In more recent studies made by the writer alone it was proved that doses of from 7 to 15 grains, when given to a dog of 20 or 30 pounds, have no action of importance (see tracings Nos. 1 and 2); but Pavlinow [1] asserts that the drug causes an increased arterial pressure and a slightly slowed and more regular pulse. On the other hand, Dujardin-Beaumetz [2] agrees with the writer, and asserts very positively that the influence exerted by medicinal doses is very slight.

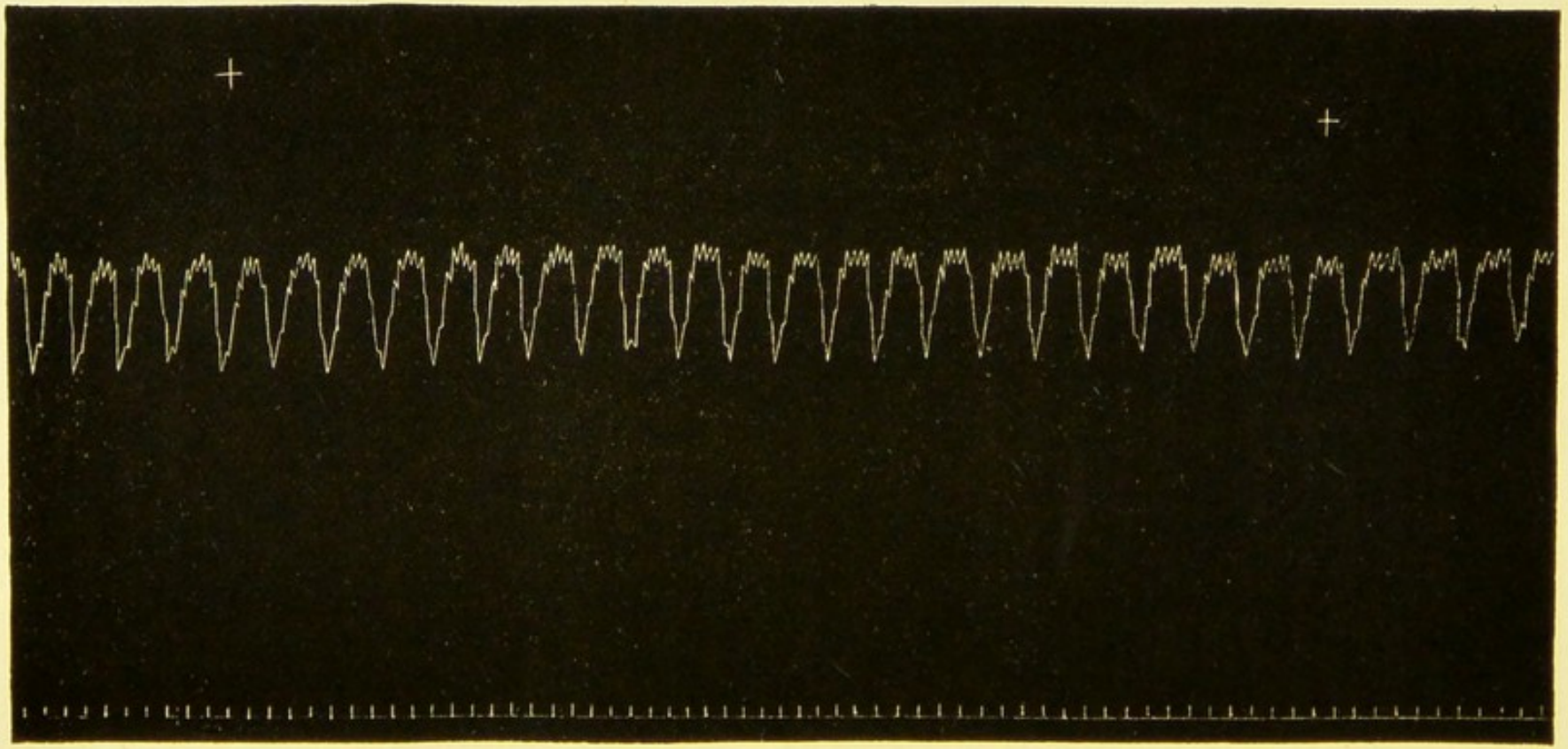
The reason for Pavlinow's contradictory results lies probably in two points, namely, that the drug used by

[1] Meditzinskoie Obozrenie, fasc. xii, 1885, p. 1203.
[2] Therapeutic Gazette, Sept. 15, 1885.

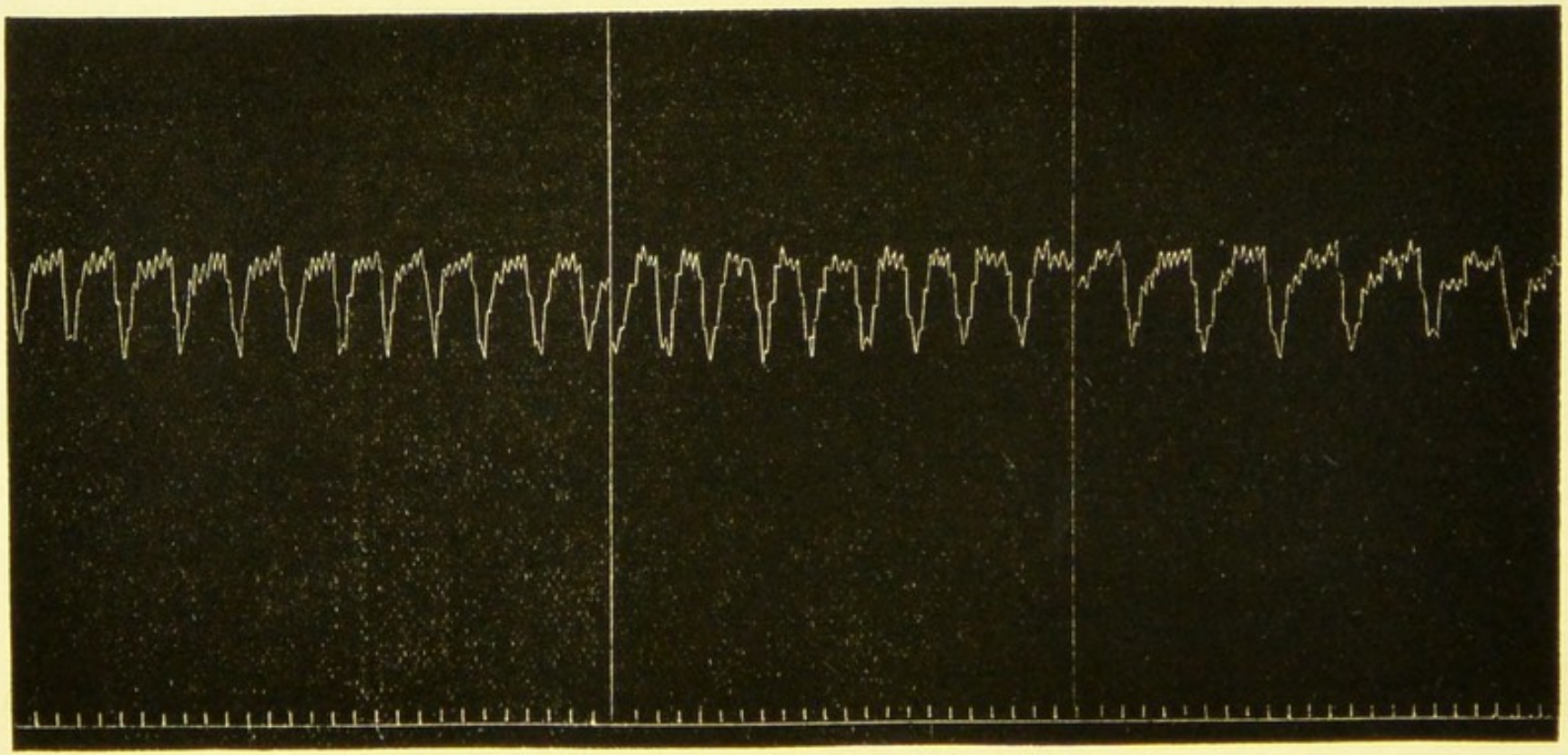
him was impure, as it was not the right color, nor was it made by Knorr, and that the doses used may not have been medicinal. This is undoubtedly the reason for the statements of Arduin[1] and Demme,[2] who used doses which were absolutely overwhelming. Thus, Arduin gave as much as 45 grains to a rabbit at one dose, and Demme gave 15 grains. The first observer noted circulatory depression and cardiac paralysis; the second, increased arterial pressure, followed by a fall, although the heart continued to act very well. The results of Devraux-Armand[3] and of Henri Casimir[4] are identical with those just quoted, and depend likewise upon the large amounts employed, for there can be no doubt that such doses can produce every form of circulatory disturbance. Notwithstanding these assertions, then, the results obtained by those persons using moderate doses positively decide that the drug is, in reality, without circulatory effect, and that any changes which are seen, clinically, depend on the alterations in temperature rather than on the drug.

When given in poisonous doses, the circulatory changes and the systemic results produced depend to some extent upon the idiosyncrasies of the animal receiving the drug. If convulsions occur, the circulation is, of course, disturbed, and the heart is finally arrested in diastole, being previously much weakened. Arduin and Demme assert that this is so in the frog, but Coppola[5] states that antipyrin has no such influence, and that the heart is unaffected in this animal. From the studies of the writer he is confident of the correctness of the statements of Arduin and Demme, and doubts

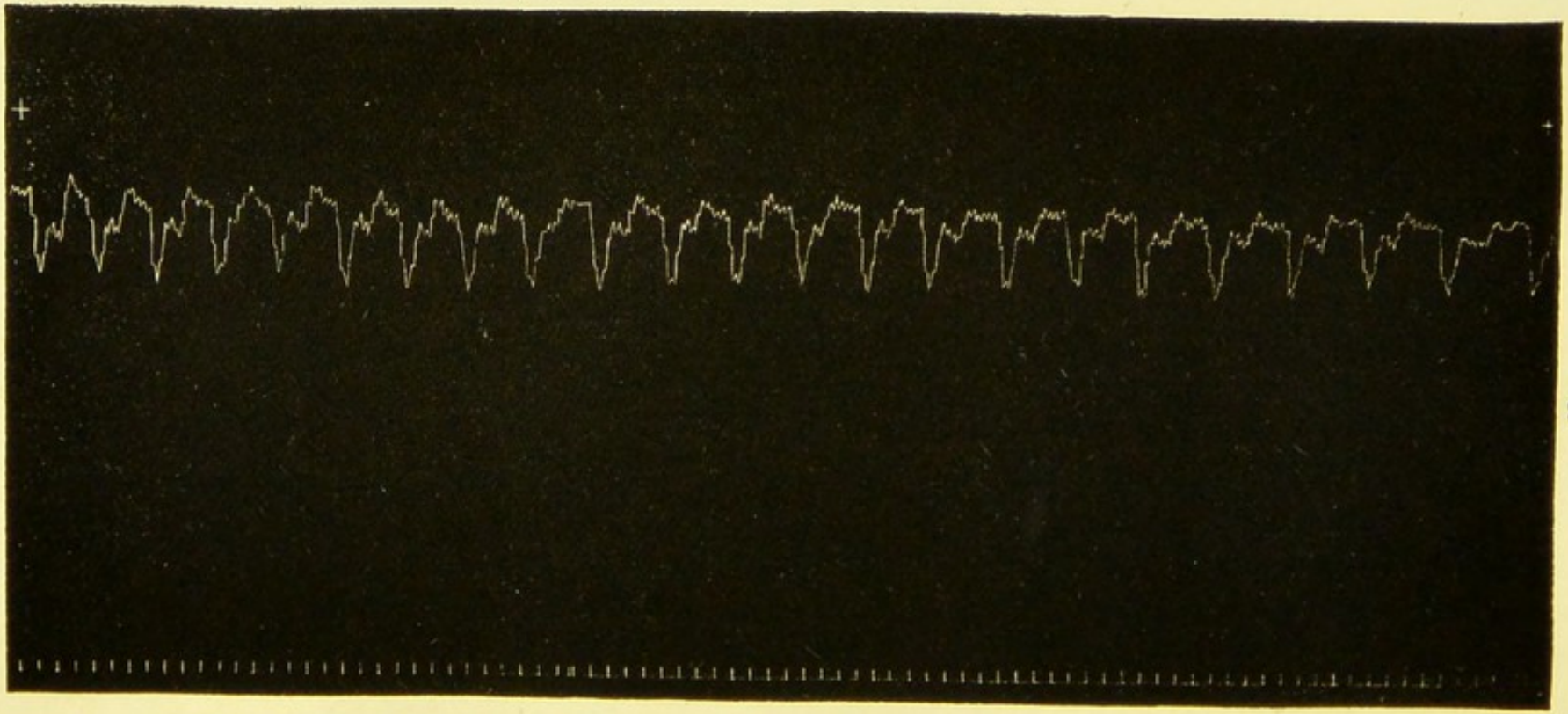
[1] Paris Thesis, 132, 1885.
[2] Fortschritte der Medicine, Bd. ii, 1884, p. 657.
[3] Thèse de Nancy, 1885.
[4] Thèse de Lyon, 1886.
[5] Koberts Jahresbericht, 1885, p. 314.



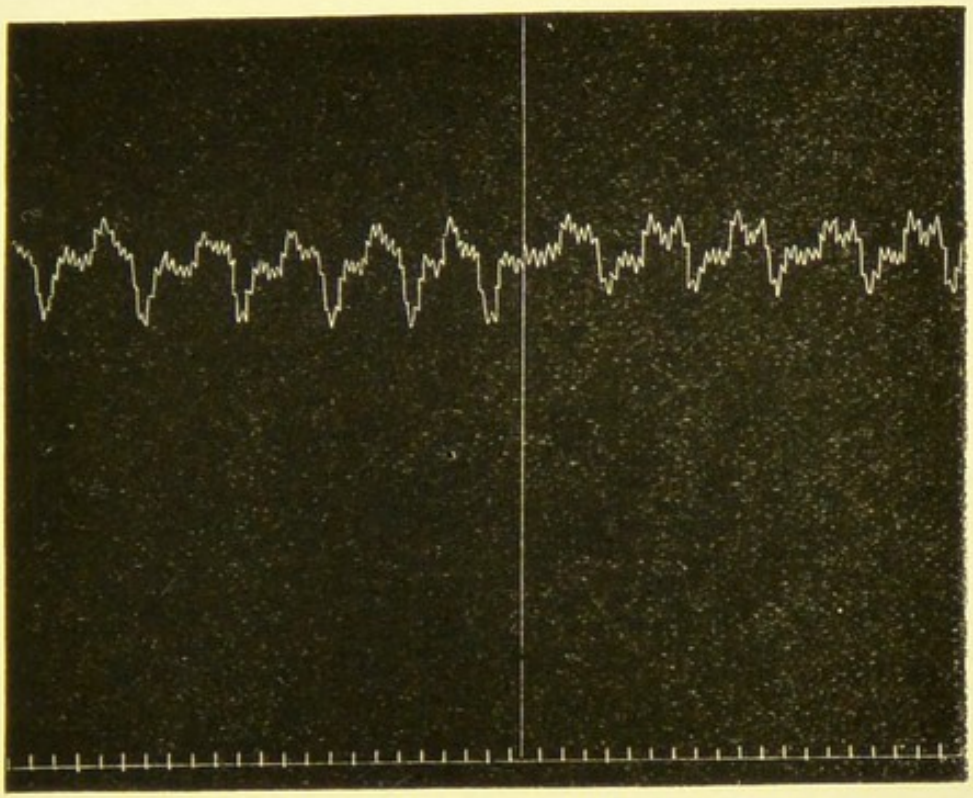
Tracing No. 1.—Dog; Weight, 24 Pounds. Injected 7½ Grains of Drug into Jugular Vein Between + Marks.



SAME CONTINUED. SIX MINUTES LATER. SIX MINUTES LATER.



TRACING No. 2.—DOG; WEIGHT 34½ POUNDS. INJECTED 15 GRAINS OF ANTIPYRIN BETWEEN + MARKS IN 15 C.CM. OF WATER.



SAME CONTINUED, TWO MINUTES LATER.

SAME, EIGHT MINUTES LATER.

those of Coppola, and the results obtained by Batten and Bokenham[1] are in direct confirmation of his opinions.

The Blood.—In no part of the study of the physiological action of a drug should greater care be taken to separate the effects of moderate and medicinal doses from those of toxic size, than in respect to this tissue. It is the carelessness of investigators in respect to these facts which so commonly gives rise to apparently contradictory results, which are in reality perfectly correct and readily adapted to each other.

There can be no doubt that antipyrin is capable of producing changes in the character of the blood, both as to its color and its corpuscular elements, provided that a sufficient amount be employed; and it is also a fact that this amount must always be large enough to pass beyond the boundary of a "medicinal dose," and be called a toxic amount. While this assertion seems paradoxical at the first sight, it is not so, in that in those who exhibit cyanosis and other evidences of poisoning, after ordinary doses, a toxic effect is in reality present, owing to idiosyncrasy. In other words, a person who is unusually susceptible to 10 grains of antipyrin is quite as much poisoned when this dose is taken as is the individual not so readily affected who exhibits symptoms of poisoning after 30 or 60 grains.

That no changes in the hæmoglobin occur, under doses given for medicinal purposes in ordinary patients or animals, seems positive, both by reason of the absence of any signs of such troubles and the result of careful spectroscopic examination. Thus, Leon Arduin[2] asserts that in his studies upon the lower animals no changes in the blood could thus be determined, and he is, therefore,

[1] British Med. Jour., June 1, 1889.
[2] Bulletin Gén. de Thérap., March 30, 1885.

in accord with Pavlinow,[1] who finds not only that this is so when antipyrin is injected into the veins, but that, in addition, no spectroscopic changes are produced, even when a 1-per-cent. solution of antipyrin is added to the blood outside the body. The writer has never seen any change in the color of the blood of an animal to whom medicinal and not toxic doses were given, and Huchard[2] has reached conclusions of a similar nature. Crolas and Hugounenq[3] also found no methæmoglobin in the blood, even after the use of from 45 to 150 grains of antipyrin a day for forty days. On the other hand, abundant evidence, both clinical and experimental, exists to prove that changes are produced by excessive amounts, particularly if any susceptibility is present. Too many instances are on record in the case of the human being in which cyanosis and a peculiar coloring of the face and surface of the body have occurred to allow of any doubt on this point, and the researches of Lepine[4] give us ample evidence of the nature of these changes, for he found that the spectroscopic bands of methæmaglobin were strongly present in the blood of animals poisoned by the drug.

These points are of more practical bearing in relation to therapeutics than would appear at first sight, in that certain writers assert that, in their opinion, the antipyretic influence of antipyrin depends upon a failure on the part of the hæmoglobin of the blood to carry to the tissues the oxygen necessary for their consumption, and that the consequent fall in fever is owing to the alteration of the hæmoglobin into the abnormal product already named.

[1] Meditzinskoie Obozrenie, fasc. xii, 1885, p. 1203.
[2] La Semaine Médicale, 1885.
[3] Lyon Médicale, March 3, 1889.
[4] Lyon Médicale, vol. liii.

If, as has been asserted,[1] the hæmatin of the blood is separated under the influence of the drug, we should have at once the appearance of this substance in the urine; and the fact that hæmoglobinuria so rarely, if ever, occurs after ordinary doses of antipyrin, proves that the drug may lower bodily heat without dissolving out or destroying the coloring matter of the blood.

The effect of antipyrin in ordinary amounts on the corpuscles themselves is of no moment, but changes naturally occur in these bodies when their coloring matter is destroyed or altered. Under such circumstances they appear somewhat shriveled, and, perhaps, crenated, but otherwise normal. That they are not much affected is proved by the researches of Crolas and Hugounenq,[2] and by those of Pisemski, of St. Petersburg.[3] The first-named investigators found that, even when from 40 to 150 grains of antipyrin are given daily for forty days, no appreciable change in the number of the corpuscles takes place. Pisemski, who poisoned his animals by smaller amounts, both dogs and rabbits, reached similar conclusions, but states that, ultimately, there may be a decrease in the number of these bodies, owing rather to the exhaustion of the animal than the direct influence of the drug.

Tissue Waste, or Bodily Metabolism.—Although fever depends primarily upon the action of disordered nervous protoplasm, it secondarily rests largely upon the destruction and repair of the tissues of the body. If the fever is high, the tissues are more rapidly destroyed, and as a result the urine, as the chief carrier of the excretions, is laden with the increased amount of nitrogenous and other matters thrown off.

[1] Bartholow, Therapeutics, 1887, p. 381.
[2] Lyon Médicale, March 3, 1889.
[3] St. Petersburg Inaug. Dissert., 1887, p. 48.

Closely following the calorimetrical studies which have been made, a number of observers have studied the effect of antipyrin upon the destruction of tissue in fever, with results which, considering the complexity of the subject and the constant variation in the body, are of unusual similarity. By far the most thorough and complete study of this subject that we have yet seen is that of Robin,[1] who has confined his attention solely to the kidneys and their secretion when antipyrin is used. Taking six healthy men, he found that when as much as from 30 to 45 grains of antipyrin were given there followed a decrease in the quantity of urine amounting to 20 or 40 per cent., and that in one or two instances this decrease was still more marked.

This result is also confirmed by Jabubowitsch[2] in the case of children, and by Dujardin-Beaumetz.[3] The urea was decreased in amount, whether the subject experimented upon was well or sick; while the uric acid was increased in healthy persons, but remained constant in amount in the sick, or else varied slightly.

The chlorides were diminished in most cases, but in one instance they were unaffected.

Wickowski has also noted a considerable diminution in the amount of the chlorides in the urine under the influence of antipyrin. Robin has found that in chronic diseases the diminution of the quantity of urine under doses of antipyrin was more marked than in acute diseases, and that the decrease was greatest in those diseases where nutrition was most affected.

The writer would not be doing justice to this subject, however, did he not point out one or two points in the

[1] Gazette Méd. de l'Algerie, Jan. 15, 1888.
[2] Jahrbuch für Kinderheilkunde, 1885, Bd. xxiii, No. 4.
[3] Therapeutic Gazette, 1885, p. 580.

method of Robin which, while they do not of necessity involve inaccuracy in result, to a certain extent endanger the worth of his conclusions. Estimates of the quantity of solids excreted by the kidneys must necessarily be surrounded by so many conditions productive of error that all experiments should be most carefully guarded against fallacies. Particularly is this the case where the influence of one or two doses of a drug is to be considered, for it is perfectly possible that the medicament may so influence the renal structure as to cause a temporary diminution of excretion, which does not necessarily indicate an actual decrease in tissue waste. Renal torpidity may show itself by decreased elimination, which passes away in the course of a short period, to be followed by the elimination not only of the tissue waste of the time being, but that of the period during which the kidney remained inactive. It is this point which Robin has overlooked, and in consequence of which his research is decreased in value.

The communication of Robin has, however, been supported by the experiments of Umbach,[1] who, having made a series of studies on himself in health under large doses of antipyrin, finds that, while the quantity of his urine was not altered, there was nevertheless a very notable decrease in the elimination of urea, and asserts that antipyrin checks tissue metamorphosis very greatly. The uric acid was not altered in quantity. His method consisted in estimating the amount of sulphuric acid and uric acid, and the total quantity of nitrogen excreted normally and under the influence of the drug.

The records of Riess[2] and of Müller,[3] from experi-

[1] Archiv für Exper. Pharmacol. und Pathol., xxi, Nos. 2 and 3.
[2] Archiv für Exper. Pharmacol. und Path., 1886, xxi.
[3] Jahresbericht für Thier-chemie, xiv.

mentation on the patients under their care, also confirm the conclusions of Robin and Umbach. Riess selected typhoid patients in the height of their fever, and, after regulating their diet most carefully and preventing the appearance of all causes calculated to disturb the elimination of tissue waste, measured with Teutonic accuracy the nitrogenous excretion during nine consecutive days, which period was separated into three divisions. During the first three days the fever was allowed to run its course untreated, for the next three days it was kept down by ordinary amounts of antipyrin, and during the last three days the fever was once more allowed to exist without treatment. It is unnecessary for the writer to enter into greater detail as to the methods employed, as they seem beyond criticism. Suffice it to state that Reiss found, in the days during which antipyrin was given, that the quantity of nitrogenous matter eliminated was decreased from 15 to 30 per cent., as compared with the days during which no drug was exhibited.

In the experiments of Müller, made upon a case under his care, it was found that the nitrogenous matters in the urine were decreased 28 per cent. when the fever was controlled by antipyrin, as compared with those given off on alternating days when no antipyrin was employed. Engel,[1] under like circumstances, has noted a decrease amounting to from 16 to 25 per cent. The same results have been reached by Wiczkowski,[2] Girard,[3] and Lahousse.[4] The last observer carried out his studies on himself, and used the methods of Kjeldahl in the estimation of the salts and other urinary con-

[1] Beiträge aus d. Wurzburger Klinic, Bd. ii, p. 146.
[2] Quoted by Umbach.
[3] Annals de la Soc. de Méd. d'Anvers Aout, 1887, p. 231.
[4] Revue Méd. de la Suisse Romande, vii, p. 642, 1887.

stituents, or, in other words, employed methods identical with those followed by Umbach.

In children, Jacubowitsch[1] asserts that the elimination of urea is greatly decreased, and condemns the use of antipyrin for this reason, and in a series of cases Walter[2] noted similar results after doses of 45 to 100 grains a day.

The evidence contradictory to the statements and researches of all the investigators just named is comparatively slight, and, while worthy of notice, probably depends upon some fallacy for its existence. Thus, we find that Crolas and Hugounenq[3] state that the quantity of urine excreted is not diminished, and that the quantity of urea is increased. They also assert that the phosphoric acid does not undergo alteration in respect to its quantity.

Pavlinow[4] also states that the amount of the urine is unchanged,—a statement indorsed by Kumagawa,[5] who, after experiments on dogs with doses of large size, finds neither a decrease nor increase in the total nitrogenous elimination per day. This last investigator did find, however, a great increase in the uric acid, which amounted to more than double the normal quantity.

Devraux-Armand[6] found a decided increase in the elimination of urea in his own case under the use of 45 grains a day of antipyrin.

In view of the very great number of persons who find a decrease in nitrogenous change after the use of antipyrin, as compared with those who do not, and considering the care exercised by many of the former class

[1] Jahrbuch für Kinderheilkunde, 1885, Bd. xxiii, No. 4.
[2] Vratsch, No. 30, 1885. [3] Lyon Médicale, March 3, 1889.
[4] Meditzinskoie Obozrenie, fasc. xii, 1885, p. 1203.
[5] London Medical Recorder, Oct. 20, 1888.
[6] Thèse de Nancy, 1885.

in their studies, it would seem that we have a right to conclude that antipyrin does decrease nitrogenous elimination, as a general rule.

Having decided that antipyrin decreases nitrogenous changes, we are at once brought face to face with the question as to whether this decrease is primary or secondary in its causation, or, in other words, is this the result of a direct influence of antipyrin, or is it simply brought about by the decrease in fever and consequent decrease in tissue waste. Umbach has, fortunately, not overlooked this question, and by making two series of experiments, one of fourteen days and one of six days, he found, in both series, that the nitrogen eliminated on antipyrin days, in himself, a healthy man, was 10 per cent. less than on normal days. That this was due to decreased waste, not to retention, is proved by the fact that on the days following the use of the drug the nitrogen gained its normal level, and no more. It seems, therefore, that the decrease is a primary one, although in fever there can be no doubt that it is also secondary.

In respect to the changes that take place in the expired air, and which give evidence of tissue metamorphosis in the body, we have for study the papers of several investigators. Livierato[1] has found a diminution in the amount of the carbonic-acid gas, and Henrijean[2] has noted in fevered animals a notable decrease in the absorption of oxygen when antipyrin is used.

In the normal rabbit, our own countrymen, Chittenden and Cummins,[3] have been unable to note any change in the elimination of carbonic acid under large

[1] Rivista Clinica di Bologna, 1885.
[2] Travaux du laboratoire de Leon Fredericq, t. i, 1885-86, pp. 288, 289.
[3] Physiol. Lab., Yale, Sheffield School, vol. ii.

or small doses, which is remarkable, in view of the fact that if very large amounts are given the hæmoglobin must be so altered as to produce some such change, without doubt.

Very closely allied to these questions is the research of Lepine,[1] who concludes that antipyrin opposes the glycogenic function of the liver, and so, at least in part, diminishes the production of heat by an influence exercised on the hepatic cells.

Nervous System.—When very large, massive doses of antipyrin (4 or 5 drachms) are injected intra-venously into one of the lower animals, the animal immediately becomes relaxed and weak, and in a moment falls to the ground, totally unable to move. Respiration becomes more and more feeble and finally ceases in death. This result, obtained by the writer, has been confirmed, in the frog, by Coppola,[2] Demme,[3] and Arduin,[4] and there can be no doubt of its correctness. Under these circumstances there is, of course, total loss of reflex activity. Blumenau has also noted a decrease in the irritability of the cerebral cortex of the dog after massive doses were used.

When smaller but poisonous doses of antipyrin are given to the dog and rabbit, or to the cat, convulsions of a tetanic type rapidly come on. The spasms are also somewhat clonic, or may be at one moment tonic and the next clonic. They are exceedingly severe, the animal being thrown hither and thither by their intensity. Consciousness seems to be preserved, though it has been proved that it is the brain which is largely acted upon by the drug under these circumstances, since section of

[1] Lyon Médicale, iii, 1889, and Arch. de Méd., exp., Jan., 1889.
[2] Kobert's Jahresbericht, 1885, p. 314.
[3] Fortschritte der Medicin., 1885, ii., 657. [4] Thèse de Paris, 1885.

the cord stops the disturbance in the lower half of the body.

The following experiment performed by the writer shows this :—

Dog ; weight, 27½ lbs. Black bull-dog, full grown.

4.05. Gave 160 grains of antipyrin by the jugular vein in about one ounce of pure water.

4.06. Seems restless.

4.07. Has just had a slight convulsion.

4.08. Another convulsion.

4.09. Convulsion after convulsion ; now tonic, now clonic ; is thrown from side to side. Twists and squirms and rolls over and over in the spasms.

4.12. Section of spinal cord at the fourth dorsal vertebra.

4.20. Fore-legs still convulsed, with head and neck ; hind-legs quiet.

4.25. Killed by chloroform.

These results are confirmed by the earlier ones of Wood,[1] Reichert, and the writer, and by Coppola, Leon-Arduin, Demme, Blumenau,[2] and Pavlinow.[3] They also receive further confirmation through the experiments of Chouppe,[4] who has found that the convulsions of antipyrin do not produce cramp asphyxia, as do the convulsions which arise purely from the spinal cord.

As one would readily suppose, from the general nervous symptoms just detailed, there are two stages, or rather states, of reflex activity. If the dose has been excessively large reflex activity is lost at once, but if it

[1] Therapeutic Gazette, 1886.

[2] Wjestnik psichiatrii i nevropatologii, 1888, v-vi. See also St. Petersburger Med. Wochenschrift, No. 52, 1887.

[3] Meditzinskoie Obozrenie, fasc. xii, 1885, p. 1203.

[4] La Semaine Médicale, July, 1887.

be only sufficient to cause convulsions the reflexes are not only preserved, but increased. Thus, Blumenau states that he has found, in the dog, cat, and frog, an increased reflex excitability to tactile and electrical stimuli, but no change in response to chemical irritation, when a convulsing dose is given, and he is confirmed by all the observers who studied the spinal action of the remedy.

Besides the state of reflex activity from poisonous doses, we have undoubtedly a state of decreased reflex action produced by medicinal doses of the drug. This decrease is not only seen clinically, but has been proved to exist by Germain-Sée and Gley,[1] as well as Lepine[2] and the writer. The first of these investigators saw in dogs a marked decrease in reflexes, to such an extent that galvanization of the sciatic nerve caused only a feeble response, and found that this was due to depression of the sensory nerves and the receptive side of the cord. Lepine has found that if the nerve in one leg be protected from the poison by ligature, it will respond much more readily to the stimuli than will that of the unprotected limb. From these researches it is evident that ample cause for decreased reflex action is present.

Practically, Chouppe has found that antipyrin tends to prevent strychnine convulsions by this depressant influence.

Respiration.—According to the writer's studies, and those of Batten and Bokenham,[3] death from antipyrin, when given in lethal doses to one of the lower animals, results from failure of the respiratory centre. In ordinary doses no change in respiration occurs, but, according to Pavlinow,[4] large doses make it more rapid. This

[1] L'Union Médicale, April 26, 1887.
[2] Lyon Médicale, liii.
[3] Lancet, June 1, 1889.
[4] *Loc. cit.*

assertion is supported by the writer's observations, and is, in his estimation, correct.

Elimination.—The elimination of antipyrin goes on very rapidly, indeed, and begins almost immediately after its ingestion. Thus, Maragliano[1] states that it appears in the urine three hours after its ingestion. At the fourth hour the elimination is at its height, and continues for twenty-four or thirty-six hours. Antipyrin is also eliminated by the salivary glands, according to Pavlinow. Pavay[2] states that antipyrin appears in the urine in one or two hours, and that the addition to this liquid of chloride of iron causes the development of a red-brown color.

Toxic Effects from Prolonged Use of Antipyrin.—So far as the writer is aware, no case of severe chronic poisoning has ever been reported as the result of antipyrin, but it is interesting to know what changes occur under such circumstances in the lower animals.

By far the most thorough research on this subject is that of Pisemski, carried out in the laboratory of Ivanovski upon healthy adult rabbits and dogs. It was found that when the drug was introduced under the skin of a rabbit in the daily dose of $7\frac{1}{2}$ grains, death ensued on from the sixteenth to the thirty-first day; or, if the dose amounted to 15 grains daily, death occurred in a few days. If the dose amounted to 23 grains, death occurred one and one-half hours after the injection. In dogs, if the daily dose was 15 grains, the animals died on the fifteenth and twentieth day, or if it amounted to 45 grains daily, death came on the succeeding day.

The chief changes noted by Pisemski at the autopsy

[1] Kobert's Jahresbericht, p. 313, 1885.
[2] Wien. Med. Wochenschrift, 1886, No. 8.

were intense engorgement of the brain and meninges, with a serous exudate into the cerebral ventricles.

The lungs were highly congested and had a bright-red hue. The spleen was small and shriveled, while the kidneys were congested and slightly inflamed. The liver was not much affected and the red blood-corpuscles were greatly decreased in number.

The lethal dose of antipyrin for the rabbit is said by Dujardin-Beaumetz to be 22 grains to every two pounds of the animal's weight.

Antiseptic Action.—According to Brouardel,[1] antipyrin exercises a very distinct antiseptic influence. On fermentation, such as seen in beer, it acts quite powerfully, delaying or preventing it. The quantity of antipyrin required was found to be below 1 per cent. to delay it and 5 per cent. to prevent it.

On the germination of seeds the drug also exercised a very marked action, delaying this process many hours.

It was also found that, added to blood, it prevented putrefaction if present in the amount of 10 per cent.

Coppola[2] has also noticed that antipyrin in 3-per-cent. solutions prevents alcoholic fermentation, as well as the action, of malt diastase.

On the alcoholic fermentation of wine a very decided inhibitory effect was produced.

Conclusions as to Physiological Action of Antipyrin.—1. Antipyrin generally lowers normal bodily temperature to some extent.

2. It lowers, to a very remarkable degree, febrile temperatures.

3. The lowering of normal bodily heat depends

[1] La Semaine Médicale, Dec. 21, 1887.

[2] Jahresbericht für Thierchemie, 1885, p. 98.

upon a lessened production of heat, followed by a decreased dissipation.

4. The same process takes place in the reduction of fever by this drug.

5. The effect upon the circulation produced by antipyrin in the normal and febrile animal is virtually *nil.*

6. Antipyrin changes the hæmoglobin of the blood into methæmoglobin only when it is given in excessive quantity. In ordinary amount it has no influence on this tissue.

7. Under its influence the quantity of urine is decreased and the urea and other evidences of tissue waste are also diminished.

8. Antipyrin diminishes reflex activity by depressing the sensory and motor tract of the cord and the motor and sensory nerves, the latter being most affected.

9. On normal respiratory movement its influence amounts to almost nothing in ordinary amount. In poisonous dose it causes death by respiratory failure.

10. It is eliminated very rapidly from the body by the kidneys.

11. Given for a great length of time in large amount, it is distinctly poisonous.

Clinical Evidence.

Turning from the experimental evidence which we possess in regard to the influence of antipyrin upon the animal economy, let us consider its use by the bedside, taking up *seriatim* the purposes for which it is employed. At the present time little doubt can exist but that it is the most reliable antipyretic substance that we have, if the fact be borne in mind that it also possesses very little power for producing serious harm to the patient, even if idiosyncrasy to it exists.

Large as is the literature of the experimental and scientific side of this subject, it is but a "drop in the bucket," as compared to the enormous mass of material which has been placed before us by almost every physician in the civilized world. For years the medical journals of every language have teemed with clinical reports, and no sooner has the value of the drug in one malady been well discussed than a host of clinicians test it and write of its use in another.

Born to the profession of medicine at a time when the medical heart was yearning for some elegant way of reducing the fever heat, which Liebermeister had so ably proved to be deleterious to the patient's welfare in prolonged fevers, antipyrin was at once seized upon and used by every practitioner with feverish haste. So rapid was its wave of progress that the medical student who had just graduated in the spring, without knowledge of the drug, found it in wide-spread use almost before he could find a spot in which to begin the practice of his profession. For this reason an attempt to embody the literature of antipyrin in any essay would be absurd; even if room for all the clinical reports could be found, they would be but dry and uninteresting reading, and it is the author's duty to gather up the good grain from the tares rather than to bring before the reader for his examination the entire crop of communications as a garnered harvest.

The writer of this essay, therefore, will confine himself solely to those points which have been made by authors whose observations are most worthy of credence, and to the results obtained by himself in the use of antipyrin in the wards of St. Agnes Hospital and elsewhere.

In order that the subject may be the more clearly understood and considered, it is, perhaps, best to divide

it into four parts, namely, the general influence of antipyrin, its influence and use in fever, its power over the nervous system, and its effects upon malarial poisoning.

General Influences.—When antipyrin is given in the dose of 10 to 20 grains to a healthy man, it produces either no symptoms at all or else a more or less well-marked ringing in the ears, accompanied with a sensation of fullness of the head. The bodily temperature varies under its influence but the fraction of a degree, and no change at all may occur.

If as much as 60 grains are taken at one dose, nausea, followed by vomiting, may at once come on, while the slight cerebral symptoms already named may become very violent. Generally, these symptoms are of short duration, but they may last for several days in persons who are susceptible to the drug. Very rarely untoward effects assert themselves in susceptible persons, but when they do occur they are as various in their forms as are the persons who have the symptoms. Aside from the results of poisonous doses, a large number of cases present slight cyanosis or duskiness of the hands and face about the nose and lips. The fingers may be cold and clammy, and the feet are often very cold. Sweating is a very common symptom of an untoward influence, and prickling or tingling of the skin is not uncommonly seen.

By far the largest number of these cases, however, suffer from disorders associated with the skin. Erythematous patches can be seen everywhere, more particularly on the hands and feet and about the face and arms, or on the chest. In some instances pemphigus-like spots appear, and even large bullæ have been noted as present.

If the reader will glance at the tables following this page, he will see how the symptoms vary, and how difficult it is to discover more than a few points common to all cases. Notwithstanding this fact, however, it is of some importance to study the results reached by an analysis of the hundred and odd cases here collected. At the very first glance, it is readily seen that the number of instances where untoward effects were present in females is largely in excess of those instances in which they occurred in males; and it is also worthy of note that the prevailing age was decidedly that of full adult life, namely, from 30 to 40 years, both in males and females, as may be seen from the following tables:—

Females.		*Males.*	
Age, 1 to 10 years,	6 cases.	Age, 1 to 10 years,	4 cases.
" 10 to 20 "	12 "	" 10 to 20 "	5 "
" 20 to 30 "	8 "	" 20 to 30 "	5 "
" 30 to 40 "	15 "	" 30 to 40 "	4 "
" 40 to 50 "	2 "	" 40 to 50 "	3 "
" 50 to 60 "	2 "	" 50 to 60 "	1 case.
" 60 to 70 "	4 "	" 60 to 70 "	1 "

Passing on, we find that the dose which caused untoward effects was generally a moderate one, and that it was from 10 to 15 grains in most instances, and next most frequently from 5 to 10 grains. It is also to be seen, on analysis, that this proportion holds good in males as well as females, although, of course, to a much less degree. A glance at the next column of the tables, that on the time of onset, will show that this species of information may be divided into two sets. One of these is when the drug was taken for a length of time before bad effects were noted; the other, when the evil effects came from a single or double dose. It will also be seen that, when single or double doses were the cause of the

UNTOWARD EFFECTS OF ANTIPYRIN, No. 1.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
20	F.	135 grs. in 9 days.	On the 8th day.	Scarlatinous rash over entire body, with desquamation preceded by blebs.	Not stated. Very slow in healing.	Recovery.	Spitz, of Breslau. Therapeut. Monatshefte, No. 9, 1887.	Not stated.	Typhoid fever.	
				Bleeding from bowel, nose, and bronchial tubes.			Pribram, of Prague. Wiener Med. Wochensch., No. 47, 1886.		Spotted typhus.	
Not stated.	Not stated.	4½ grs. at one dose.	In 5 minutes.	Coryza; reddening of the face; lachrymation; abundant expectoration; profuse sweating; urticaria, and rapid pulse.	¾ hour.	Recovery.	Sturge. British Med. Journal, Feb. 4, 1888.	Not stated.	Migraine.	
21	M.	30 grs. at one dose.*	In a few minutes.	Dyspnœa; labored cardiac action; deep cyanosis; rapid pulse.	½ hour.	Recovery.	Guttmann. Therapeut. Monatshefte, No. 6, 1887.	Not stated.	Acute articular rheumatism.	
21	F.	15 grs. at one dose.	In 5 minutes.	Heat and burning, with severe itching over the entire body; urticaria on the face; labored cardiac action and momentary amaurosis; œdema of face and hands came on in half hour; sugar and albumen in urine.	3 days.	Recovery.	Guttmann. Therapeut. Monatshefte, Feb. 4, 1887.	Not stated.	Migraine.	

* This same case took, five weeks later, 75 grains of antipyrin in five hours without bad effect.

UNTOWARD EFFECTS OF ANTIPYRIN, No. 2.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
20	M.	From 30 to 75 grs. a day for 14 days.	After last dose.	A chill, followed by a rise in temperature of 2.4° C. in two hours, also a scarlatinous rash; on third day fever fell.	Three days.	Recovery.	Laache. Centralblatt f. klinische Medicin., 1886, vii, 32; Schmidt's Jahrbücher, Bd. 211, p. 250.	Not stated.	Phthisis.	
39	M.	75 grs. a day for 6 days.	On 6th day.	Temperature rose to 40° C., and remained there; rash over body.	Not stated.	Recovery.	Fraenkel. Deutsche Med. Wochensch., Nos. 43 and 44, 1886.	Not stated.	Articular rheumatism.	
52	F.	30 to 60 grs. a day for 8 days.	On the 8th day.	An intense onset of fever; later, a severe pain in breast, in stomach, and abdomen; cold sweat and rash on skin.	Not stated.	Recovery.	Bernoulli, of Basel. Correspondenzblatt für Schweizer-aerzte, 1887, p. 357.	Not stated.	Articular rheumatism.	
10	F.	11½ grs. at a dose for 1 day.	At once.	Giddiness and a rash; seemed as if drunk; temperature very high.	Not clearly stated.	Recovery.	Mueller, of Zurich. Correspondenzblatt für Schweizer-aerzte, 1888, p. 685.	Not stated, but delicate.	Acute rheumatism.	Heart was not affected by disease.
35	F.	35 grs., followed in 3 hours by 17 grs.	At once.	Temperature at 103.6° F.; fell to 98°, and death followed in thirty-two hours.	32 hours.	Death.	Barr. Lancet, London, Feb. 28, 1885.	Not stated.	Puerperal fever.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 3.

AGE.	SEX.	DOSE.	TIME OF ONSET.	SYMPTOMS.	DURATION.	RESULT.	BY WHOM AND WHERE REPORTED.	TEMPERAMENT.	DISEASE.	REMARKS.
28	F.	15 grs. at one dose.	After one dose.	Severe burning pain in stomach, vomiting, and marked signs of collapse; cyanosis of face; rash on skin, with irritation.	1 day.	Recovery.	RAPIN. Centralblatt für klin. Med., May 11, 1889. Also, Revue Méd de la Suisse Romande, 1888, November 20th.	Not stated.	Sciatica.	Had often taken it before.
				In 6 cases a rash was produced, and in 1 a purpuric state.			DRAPER. Med. News, April 11, 1885, p. 409.	Not stated.	Typhoid fever.	
Young woman	F.	15 grs. in divided doses.	At once.	Low temperature; vomiting; cyanosis; embarrassed respiration.	Not stated.	Recovery.	Journal de Méd. de Paris, May 29, 1887.	Not stated.	Typhoid fever.	8th month of pregnancy.
Adult.	F.	7 grs. at one dose.	At once.	Fear of death; watery eyes and suffused face; difficult respiration; pain over heart; headache.	"Gradually wore off."	Recovery.	WEIR. Medical News, Aug. 6, 1887, p. 166.	Not stated, but nervous.	Nervous headache.	Same symptoms occurred twice afterward.
		30 grs. at once.	At once.	Rise of temperature of more than 1° F.	Not stated.	Recovery.	WETTERDAL. Lancet, July 9, 1887.	Not stated.	Fever.	
3	M.	4¼ grs. every hour.	4th day.	Eruption like measles all over body.	1 day.	Recovery.	DEMME. Wiener Med. Presse, July 17, 1887.	Not stated.	Thermic fever.	
Young woman	F.	7½ grs. twice at intervals of 5 hours.	At once.	Temperature fell to 94.1° F.; cramps; aphasia; dim vision; intellectual depression.	1 day.	Recovery.	CHERON. Journal de Médecine, July 31, 1887.	Not stated.	Typhoid fever.	7th month of pregnancy repeated dose; the same signs.

UNTOWARD EFFECTS OF ANTIPYRIN, No. 4.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
Adult.	F.	10 grs. in one dose.	At once.	Profuse sweating; collapse; pallor of hands and face; rapid pulse.	5 days.	Death.	Welch. Medical News, Jan. 2, 1886.	Not stated.	Typhoid fever.	Death due as much to typhoid as drug.
		20 or 30 grs.	After 1 dose.	Symptoms of collapse in all 5 cases.	Not stated.	Recovery.	Mason. Boston Medical and Surgical Journal, Dec. 3, 1885, p. 535.	Not stated.	Typhoid fever.	
17	F.	20 grs. in one dose.	At once.	Severe collapse; cyanosis and dyspnœa; weak pulse.	Symptoms after a few hours passed off.	Recovery.	Mason. Boston Medical and Surgical Journal, Dec. 3, 1885, p. 537.	Not stated.	Typhoid fever.	
45	F.	12 grs. every 3 hours.	At once.	State of collapse; pulse very feeble; purpuric spots on back.	Several days.	Recovery.	Graham. Bost. Med. and Surg. Jour., March 18, 1886.	Not stated.	Typhoid fever.	
				Rise in temperature: fatty degeneration of kidneys.		Death.	Porter. New York Medical Journ., July 30, 1887.	Not stated.	Rheumatism	
52	F.	38 to 60 grs. a day for 7 days, afterward 15 grs.	In 3 or 4 minutes.	Severe pain in chest and abdomen; mental anxiety; cold sweat and great rise of temperature; rash all over body; vomiting.	A few days.	Recovery.	Bernoulle. Brit. Med. Journal, Aug. 20, 1887.	Strong and well nourished.	Chronic rheumatic arthritis.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 5.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
12	F.	450 grs. in 9 days.	On 10th day.	Exanthematous rash over body.	A few hours.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
33	F.	810 grs. in 9 days.	On 9th day.	Exanthematous rash all over body.	A few hours.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
37	F.	450 grs. in 8 days.	On the 11th day.	Exanthematous rash over entire body.	A few hours.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
67	F.	465 grs. in 9 weeks.	Two days after last dose.	Exanthematous rash over body.	A few hours.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
19	F.	480 grs. in 10 days.	At once after last dose.	Exanthematous rash on arms and body.	A few hours.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
30	F.	480 grs. in 9 days.	After last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Pneumonia.	
23	M.	585 grs. in 10 days.	After last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
10	M.	430 grs. in 8 days.	After last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
40	M.	630 grs. in 11 days.	After the last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	None.
18	M.	90 grs. in 1 day.	After the last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
34	M.	720 grs. in 8 days.	After the last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	Very severe attack.
44	M.	150 grs. in 3 days.	After last dose.	Exanthematous rash over body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
20	M.	330 grs. in 11 days.	24 hours after last dose.	Exanthem over the entire body in 24 hours, of a hæmorrhagic type.	2 days.	Recovery.	Pusinelli. Deutsche Med. Woch., 1885, Nos. 10 and 11.	Not stated.	Typhus fever.	
Adult.		Not stated.	16th day after drug was first given.	Hæmorrhagic exanthema all over body.	Not stated.	Death.	Pusinelli. Deutsche Med. Woch., 1885, Nos. 10 and 11.	Not stated.	Pneumonia.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 7.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
16	F.	450 grs. in 9 days.	On 10th day.	Exanthematous rash over entire body.	Short.	Recovery.	Welt. Archiv f. klin. Med., February, 1886.	Not stated.	Typhoid fever.	
Not stated.	Not stated.	Not stated.	Not stated.	Profuse sweats and depression; morbillic eruption.	Short.	Recovery.	Laure. Revue Mensuelle des Malades de l'Enfance, February, 1886.	Not stated.	Not stated.	
Not stated.	Not stated.	Not stated.	Not stated.	Profuse sweat; chill; collapse.	Very short.	Recovery.	Reihlen. Deutsche Arch. f. klin. Med., April 22, 1886.	Not stated.	Typhoid.	
10	M.	330 grs. altogether.	After last dose.	A general erythematous eruption over entire body.	Not stated.	Recovery.	Ernst. Bull. Gén. de Thérap., October 30, 1884.	Not stated.	Typhoid.	
67	F.	170 grs. in 4 days.	After last dose.	Exanthem over body; measly eruption.	About 1 day.	Recovery.	Ernst. Bull. Gén. de Thérap., October 30, 1884.	Not stated.	Typhoid.	
25	M.	90 grs. in 3 days.	After last dose.	Collapse; profuse sweat; extremities cold.	Short.	Recovery.	May. Deutsche Med. Woch., June 19, 1884.	Not stated.	Croupous pneumonia.	
		360 grs. in 10 days.	Suddenly, without warning.	Erythematous eruption over entire body.	Till withdrawal of drug.		Journal de Médecine, No. 4, 1885.	Not stated.	Typhoid fever.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 8.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
		420 grs.	At once.	Erythematous eruption all over body.			Journal de Médecine, No. 4, 1885.		Phthisis.	
Adult.		45 grs. in one dose: after 37½ grs.	At once.	Collapse: subnormal temperature; irregular cardiac action: weak voice; purpura on back.	Brief.	Recovery.	Strauss. Berlin. klin. Woch., Aug. 31, 1885; Deutsche Med. Zeit., November, 1885.	Not stated.	Typhoid.	In second week.
				Albuminuria.	Brief.	Recovery.	Tullio. Bull. Gén. de Thérap., Sept. 15, 1888.	Not stated.	Chronic articular rheumatism.	
	Young girl.	7½ grs. in one dose.	In 2 minutes.	Severe gastric pains, followed by a general urticaria and unconsciousness.	Brief.	Recovery.	Whitehouse. New York Medical Record, Dec. 3, 1887.	Not stated.	Not stated.	
67	F.	37½ grs. a day for 8 days.	After last dose.	Erythematous patches on arms; eyes uncomfortable; feet cold; nausea; face red and swollen; the eyelids closed.	A few days.	Recovery.	Jennings. Lancet, Feb. 25, 1888.	Not stated.	Rheumatoid arthritis.	Peculiar heart; only beats 35 per minute normally.
Adult.	F.	75 grs. a day.	At once.	Rocking to and fro of body; lack of intelligence; gastro-enteritis.	6 weeks.	Recovery.	Jennings. Lancet, Feb. 25, 1888.	Not stated.	Rheumatism	
Adult.	F.	Not stated.	Not stated.	Throat greatly swollen; red spots on skin; profuse sweat.	Not stated.	Recovery.	Jennings. Lancet, Feb. 25, 1888.	Not stated.	Not stated.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 9.

AGE.	SEX.	DOSE.	TIME OF ONSET.	SYMPTOMS.	DURATION.	RESULT.	BY WHOM AND WHERE REPORTED.	TEMPERAMENT.	DISEASE.	REMARKS.
Adult.		10 doses of 15 grs. in 10 days.	At once, after 10 days.	Papular eruption all over body, afterward went on into erythematous blotches.	10 days.	Recovery.	CLAREMONT. British Med. Journal, October 27, 1888.	Not stated.	Typhoid fever.	
Adult.		15-gr. doses twice a day for 15 days.	Twentieth day.	Erythematous rash over entire body.	4 days.	Recovery.	CLAREMONT. British Med. Journal, October 27, 1888.	Not stated.	Typhoid fever.	
22	F.	30 grs. every hour for 3 days.	After 3 days.	Reddish eruption over body; desquamation after several days.	Several days.	Recovery.	SPITZ. Ann. de Derm. et de Syph., vol. ix, 1888, p. 192.	Not stated.	Typhoid fever.	
Adult.	F.	5 grains.	At once.	Collapse and cardiac failure; great weakness; cyanosis.	Short.	Recovery.	WILSON. Phila. Med. Times, October 15, 1887.	A large, fat woman.	Had a very weak heart.	
40	M.	Not stated.	At once.	Serious collapse and depression.	Short.	Recovery.	HAYS. New York Med. Jour., January 22, 1887.	Not stated.	Acute articular rheumatism.	
10	M.	10 grs. every 4 hours for a week.	After last dose.	Serious collapse: subnormal temperature; unconscious.	Some hours.	Recovery.	HAYS. New York Med. Jour., January 22, 1887.	Not stated.	Typhoid fever.	
8	F.	10 grs. every 4 hours.	After the last dose.	Unconsciousness; coma; subnormal temperature.	Some hours.	Recovery.	HAYS. New York Med. Jour., 1887.	Typhoid fever.		
9	Not stated.	10 grs. in one dose.	After the first dose.	Collapse: a feeble pulse; cyanosis; cold extremities; nausea.	Very brief.	Recovery.	BROOKS. Phila. Med. Times, September 3, 1887.	Not stated.	Typhoid fever.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 10.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
18	F.	10 grs. twice in 1 hour.	At once.	Severe collapse; cold extremities; cyanosis.	Very brief.	Recovery.	Brooks. Phila. Medical Times, September 3, 1887.	Not stated.	Typhoid fever.	
		15 grs. in divided doses.	At once.	Severe collapse, vomiting, and cyanosis.		Recovery.	Jour. de Méd. de Paris, 1887.		Typhoid fever.	
72	M.	15 grs. in one dose.	Immediately.	Headache, dizziness, and pain in all the limbs.	Short.	Recovery.	Seifert. Centralb. f. klin. Med., 1887.	Not stated.	Hemicrania.	
Adult.		Not stated.	Immediate.	A rash resembling measles; most marked on extremities.	24 hours.	Recovery.	Dalby. British Med. Jour., January 15, 1887.	Not stated.	Not stated.	
Adult.		Not stated.	At once.	A rash resembling measles; marked on extremities.		Recovery.	Dalby. British Med. Jour., 1887.	Not stated.	Not stated.	
Adult.		1 ounce in 8 days.	After 8th day.	Rash over body, arms, and legs.	5 days.	Recovery.	Paget. British Med. Jour., vol. i, p. 210, 1887.	Not stated.	Typhoid fever.	
							Eloy. Rev. Gén. de clinique et Thérap., Mar. 1, 1888.			
							Huchard. Jour. Am. Med. Association, July 7, 1888.			
				Collapse and depression in pneumonia.		Recovery.	D'Espine. British Med. Jour., October 6, 1888.			

UNTOWARD EFFECTS OF ANTIPYRIN, No. 11.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
							Mayor. British Med. Journal, October 6, 1888.			
		15 grs. in one dose.	At once.	Œdema of face; dryness of throat; great dyspnœa.		Recovery.	Grognot. Bull. Gén. de Thérap., Aug. 15, 1888.	Not stated.		
60	F.	7½ grs. hypodermically.	At once.	Papular exanthem over body, looking like herpes zoster.	Short.	Recovery.	Mazzotti. Giornale italiano delle malattie veneree e della pelle, June, 1888; also Progrès Médicale, September 1, 1888.	Not stated.	Sciatica.	Hypodermic injections.
		Given for two weeks.	During use of drug.	Cachectic purpura and debility.	Two weeks.	Death.	Péter. Le Bulletin Médicale, April 25, 1888.	Not stated.	Typhoid fever.	
				Uræmic symptoms, eclampsia, and death.		Death.	Péter. Le Bulletin Médicale, April 25, 1888.	Not stated.	Typhoid fever.	Perhaps not due to drug.
Child, 6		3¾ grs. every 45 minutes, for 4 doses.	At once.	Temperature fell to 95° F.; cyanosis; unconsciousness.		Recovery.	Loebl. Wiener Med Presse, January 22, 1888.	Not stated.	Typhoid fever.	
		5 grs. at one dose.	At once.	Intense itching, burning, and tingling sensation, but no rash.		Recovery.	Dutt. Brit. Med. Journal, May 26, 1888.	Not stated.		Observer's own case; repeated once.
Adult.	F.	15 grs. at one dose.	In 8 minutes.	Violent sneezing; catarrh of eyes and nose; tightness about throat; aphonia; dyspnœa.	Short.	Recovery.	Robb. Lancet, July 28, 1888.	Not stated.	Migraine.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 12.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
		10 grs. in one dose.	At once.	Intense burning in nose, mouth, eyes, ears, and throat; sneezing; copious mucous discharge from nose and lungs.	About 24 hours.	Recovery.	Peters. Medical Register, March 24, 1888.			
						Death.	Mollière. Lyon Médicale, February 19, 1888.			
	Adults		During use of drug.	Scarlatinous rashes seen in 3 cases.	Short time.	Recovery.	Wilson, Jour. of Nervous and Mental Diseases, p. 40, 1888.		Pain.	
		8 grs. in one dose.		Great coryza; irritation of larynx and cough.		Recovery.	Taylor. Brit. Med. Journal, vol. i, p. 695, 1888.			
		8 grs. in one dose.		Severe coryza and laryngeal cough.		Recovery.	Taylor. British Med. Journal, vol. i, p. 695, 1888.			
		3 doses a day for 12 days.		Wide-spread urticaria.		Recovery.	MacDonald. British Med. Journal, February 11, 1888.		Typhoid fever.	
				Scarlatinous eruption over whole body; anorexia.	12 days.	Recovery.	Hardy. La Semaine Médicale, February 22, 1888.			
				Herpetic eruption and collapse.			Oliver. Lancet, May 5, 1888.			

UNTOWARD EFFECTS OF ANTIPYRIN, No. 13.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
10	F.	8 grs. at once.	At once.	Collapse and low pulse.	Short.	Recovery.	Payne. North Carolina Med. Journal, May, 1888.	Not stated.	Not stated.	
10	F.	2 doses of 10 grs.	At once.	Dangerous collapse.	Very short.	Death.	Sykes. North Carolina Med. Journal, May, 1888.	Not stated.	Not stated.	
Child.	F.	10 grs. in one or two doses.	At once.	Coma, with collapse and sweat.	Very short.	Recovery.	Sykes. North Carolina Med. Journal, May, 1888.	Not stated.	Not stated.	
		30 to 45 grs. in 24 hours.	After three doses.	A general miliary eruption all over body.	Short.	Recovery.	Ory. Journal de Méd. de Paris, March 18, 1888.	Not stated.	Gout.	
						Recovery.	Drasche. Wiener klin. Woch., October 18, 1888.	Not stated.		
Child.	F.	5 grs. in one dose.	At once.	Urticarial rash, giddiness, and cold extremities.	Very brief.	Recovery.	Bokenham. Practitioner, April, 1888.	Not stated.	Rheumatic chorea.	
9	F.	5 grs. for 3 days.	On third day.	Urticarial rash; giddiness; drowsy.	Brief.	Recovery.	Bokenham. Practitioner, April, 1888.	Not stated.	Chorea.	
9	F.	20 grs. t. d. for 15 days.	On 15th day.	Giddiness; difficult breathing; drowsiness and delirium.	2 days.	Recovery.	Bokenham. Practitioner, April, 1888.	Not stated.	Chorea.	
Adult.	F.	3 grs. in one dose.	At once.	Giddiness and coldness of extremities.	A few hours.	Recovery.	Bokenham. Practitioner, April, '88.	Not stated.	Headache.	

UNTOWARD EFFECTS OF ANTIPYRIN, No. 14.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
				Symptoms of intoxication in females.	Short.	Recovery.	Forsbrook. Lancet, Dec. 10, 1887.	Not stated.	Migraine.	
10	F.	30 grs. a day for 21 days.	On last day.	General erythema: after local and general use.	24 to 48 hours.	Recovery.	Cehak. Allgemeine Wien. Med. Zeitung, No. 26, 1888.	Not stated.	Chorea.	
Adult.	F.	15 grs. in one dose.	In 5 minutes.	Sneezing; dyspnœa; anxiety; swelling of lids and palate.	1 day.	Recovery.	Cehak. Allgemeine Wiener Med. Zeitung.	Not stated.	Headache.	
22	F.	Not stated.	Not stated.	Reddening of skin of the body.	Not stated.	Recovery.	Wossidlo. Berliner klin. Woch., May 7, 1888.	Not stated.	Asthma.	
Adult.	M.	7½ grs. every 15 min. till 30 grs. taken.	After last dose.	Rise of temperature, with tube-casts in urine; chattering of teeth and chill.	1 day.	Recovery.	Roulin. Jour. de Méd. de Paris, June 10, 1888.	Not stated.	Neuralgic headache.	Rise of temp., sup. to be due to absorption of leucomaines.
				Collapse; all fever.		Recovery.	Bungenroth. Archiv f. Pediatrics, June, 1887.	Not stated.	Fever.	
Infant		10 grs. five times every half hour.	After 5th dose.	Vomiting and complete suppression of urine.	24 hours.	Recovery.	Haven, Boston Med. and Surgical Journal, December 3, 1885.	Infant.	Pneumonia.	Given by mistake.
							Heinzelmann. Münch. Med. Woch., 1887, No. 3.			

UNTOWARD EFFECTS OF ANTIPYRIN, No. 15.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
27	F.	1 ounce in 14 days.	On 15th day.	Measly rash, with a rigor and rise of temperature; purpuric spots on neck, which desquamated.	A few days.	Recovery.	Schwarz. Münch. Med. Woch., January 25, 1887.	Not stated.		
	Girl.	45 grs. a day for 3 days.	On 3d day.	Drowsiness, giddiness, and finally delirium; slow and labored breathing.	5 hours.	Recovery.	Batten and Bokenham, British Med. Jour., June 1, 1889.	Not stated.	Chorea.	
44	F.	15 grs. in one dose.	At once.	Sneezing; unconsciousness; face pale; jaw dropped; retching.	Not over it for a week.	Recovery.	Northrup. Medical News, April 27, 1889, p. 461.	Nervous.	Nervous headache.	
			Not stated.	Eruption like scarlet fever.	Not stated.	Recovery.	Wolf. Therapeutic Gazette, 1886, p. 413.	Invalid.	Phthisis.	
Adult.	F.	15 grs. in one dose.	At once.	Arrest of menstruation; chill; cyanosis; syncope.	1 hour.	Recovery.	Huchard. Rev. Gén. de Clinique et de Thér., Jan. 24, '89.	Woman was menstruating.	Dysmenorrhœa.	
50	M.	5 grs. in one dose.	Instantly.	Tingling and burning in mouth; blindness; pin-pricking sensation over whole body.	1 day.	Recovery.	Brit. Med. Journal, June 15, 1889.	Not stated.	Sciatica.	
				Grave collapse; profuse sweats and depression.		Recovery.	Geier. Berliner klin. Woch., November 6, 1884.	Not stated.		

UNTOWARD EFFECTS OF ANTIPYRIN, No. 16.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
28	M.	7 grs. t. d. and later 12 grs. t. d.	3 days after large doses were used.	Erythematous rash of a dark-red color; vesicles.	As long as drug was used.	Recovery.	Bloomfield. Practitioner, April, 1886.	Not stated.	Acute phthisis.	
Young adult.	M.	Not stated.	Not stated.	Erythematous rash of a dark-red color; vesicles.	Not stated.	Recovery.	Bloomfield. Practitioner, April, 1886.	Not stated.	Phthisis and alcoholism.	
27	F.	555 grs. in 5 days.	After 5th day.	Exanthem like prurigo over arms and body; collapse.	5 days.	Recovery.	Spitz, Ann. de Derm. et de Syphilog., vol. ix, 1888, p. 192.	Not stated.	Typhoid.	
Adult.	M.	15 grs. at one dose.	In 5 minutes.	Pain furious in jaw; flood of tears; headache.	Several hours.	Recovery.	Brandenburg. Brit. Med. Journal, December 15, 1888.	Not stated.	Sciatica.	
	Not stated.	Not stated.	Not stated.	Erythematous rash over body; burning of skin; like scarl. fever.	Not stated.	Recovery.	Tisne. Jour. de Méd. de Paris, 1888, vol. ii.	Not stated.	Not stated.	
	Not stated.	Not stated.	Not stated.	Profuse sweat; depressed heart; cold extremities.	Not stated.	Recovery.	McQuaid. Medical World, 1888.	Not stated.	Typhoid fever.	
Adult.	F.	15 grs. at 2-hour intervals.	Not stated.	Great collapse; fall of temperature.	Not stated.	Recovery.	Tyfaud. Jour. de Méd. de Paris, 1887, No. 22.	Not stated.	Typhoid fever.	
28	F.	3½ grs. twice, 1 hour apart.	Not stated.	Great cyanosis; pulse slow; headache.	Not stated clearly.	Recovery.	Brieger. Therap. Monatshefte, August, 1889.	Not stated.	Migraine.	

trouble, the onset was, in a very large percentage of the cases, immediate. Where the dose of the drug had been frequently repeated, it will be noted that the onset was also sudden rather than gradual. As a rule, the duration of the symptoms did not exceed three hours, and three days is the longest time mentioned for the continuance of the bad effects; while one hour was often the length of time during which serious effects were felt.

As yet, however, we have not come to the part of the subject which, after all, is the most important to the practitioner of medicine and to the patient also, and is, in consequence, the most interesting part of the question before us. In the hundred and odd cases here gathered in which the drug produced evil results, only 6 proved fatal, and in these there was ample cause for death aside from any effect of the drug. In one case puerperal fever was present in an aggravated form, in another fatty kidneys were found at the autopsy, while in the third and fourth typhoid fever was present. In the remaining 2 cases the reporters state that death was not certainly due to the drug, and perhaps would have occurred with equal rapidity if no antipyrin had been given. We can rest assured, therefore, in ordinary cases of disease occurring in patients who exhibit untoward effects of antipyrin, that, even though the symptoms be most alarming, they so rarely end in death as to enable us to rid ourselves of alarm and quiet the fears of the patient's friends.

A very interesting question in relation to the untoward effects of antipyrin is the disease in which they most frequently assert themselves. On examining these statistics, we find that it is in typhoid fever, in which the system is ever at a point at which it is susceptible

of external influence, that the symptoms unwished for have most frequently appeared. This may be partly due to the fact that the drug has been given more largely in this disease than in any other.

The record stands thus:—

Typhoid fever,	42 cases.	Puerperal fever,	1 case.
Articular rheumatism,	7 "	Sciatica,	4 cases.
Chronic rheumatism,	2 "	"Fever,"	2 "
Migraine,	5 "	Thermic fever,	1 case.
"Nervous headache,"	5 "	Not stated,	19 cases.
"Pain,"	1 case.	Neuralgia,	none.
Phthisis,	5 cases.	Pneumonia,	4 cases.
Dysmenorrhœa,	1 case.	Chorea,	5 "
Typhus fever,	2 cases.	Rheumatoid arthritis,	1 case.
Heart disease,	1 case.	Gout,	1 "
Asthma,	1 "		

Unfortunately, owing to the carelessness of the original reporters, information, in a sufficient number of cases to be of any value, cannot be obtained as to the occupations and temperaments of the sufferers.

It is impossible to give in detail all the references to the use of antipyrin in the diseases in which it has been employed. One can but give the gist of the papers which have made the epoch-markings in its therapeutic progress, and thus embody in a short space the opinions of those best qualified to speak of the matter in hand.

A very exhaustive paper, one of the best which have been published, is that of Reihlen,[1] of Nuremberg, embodying the results of a careful study of no less than 89 cases, of which 29 were suffering from typhoid fever, 16 from croupous pneumonia, 11 from facial erysipelas, 10 from acute articular rheumatism, 7 from pulmonary phthisis, and the remainder from various diseases, such as malaria and similar affections. In all of these 89

[1] Deutsche Arch. für klin. Medicin., April 22, 1886.

cases antipyrin never failed to lower the fever present within the first hour, and on no occasion was the fall so slight as to be useless from a therapeutic point of view. Aside from the fact that the degree of hyperpyrexia, rate of absorption, and dose are all determining factors in the rapidity and extent of its effects, the use of antipyrin is governed, according to Reihlen, by the age, sex, and constitution of the patient, by the method of administration, and by the other measures adopted for the relief of the patient. It was also found that the mode of giving the daily amount and the nature and stage of the disease had much to do with the fall. The weaker the patient, the more powerful is the drug for reducing fever. A very important point which Reihlen calls attention to is the fact that if the action of antipyrin becomes associated with a spontaneous fall of temperature, as at the crisis of a disease, the resulting reduction of bodily heat is colossal, and collapse often ensues. Unless the amount of antipyrin reaches 25 or 30 grains, Reihlen thinks the drug lacks the power of lowering the temperature before the disease reaches its pyrexial acme.

A very interesting assertion is made by Reihlen, namely, that tuberculous diseases, or complications, render the antipyretic action of antipyrin very powerful, and so frequently did this observer note this that he suspects tubercular change in every case of fever which is peculiarly susceptible to the drug. Contrary to the assertions of Demme, Reihlen thinks that hourly doses are much more efficacious than single daily administrations, and he gives as much as 100 grains in divided doses whenever necessary. Reihlen makes one assertion, however, from which we must distinctly differ, namely, that antipyrin affects the heart as constantly as the

temperature,—an assertion which is untrue, in that the drug does not do this directly, but indirectly,—a subject of which the writer has already spoken in the general consideration of antipyretics in the preceding pages of this essay. This is proved by Reihlen himself, who states that the fall of pulse is *pari passu* with the fall of temperature, and that the rise of pulse-rate and temperature also go hand in hand. Again, he states that in the afebrile cases, where antipyrin was given, the pulse remained unaltered,—a clinical proof of the truth of this assertion. Although von Noorden,[1] Demme,[2] and Cahn[3] also noted changes identical with those named by Reihlen, there can be no doubt that they were dependent on the fever, and not on the drug.

On the general systemic condition under antipyrin Penzoldt[4] gives us very positive opinions. He states that in children the general condition is greatly improved by the use of the drug. They appear to be more lively, sleep better, and cough less. This was the conclusion reached by those physicians who gave the drug during the great measles epidemic of 1884, in Nuremburg.

Other observers are not, however, universally in accord with these clinicians. Thus, May found only three cases, out of a large number, which were improved by antipyrin, and Alexander[5] saw but one such instance. More than this, Ernst,[6] of Zurich, speaking of the great epidemic of typhoid fever in 1884, states that "it is once more proven how little is sometimes accomplished by a mere apyresis, delirium and other symptoms taking

[1] Berliner klin Wochenschrift, 1884, No. 32.
[2] Fortschritte der Medicin., Nos. 20 and 21, 1886.
[3] Berliner klin. Wochenschrift, 1886.
[4] *Ibid.*, 1884, No. 30.
[5] Breslauer Arztl. Zeitschrift, 1884, No. 11.
[6] Bulletin Gén. de Thérapeutique, Oct. 4, 1884.

their course, as usual." Reihlen is also in accord with Ernst in this, and these assertions are, therefore, interestingly opposed to those of Liebermeister,[1] who regards the increase of temperature not only as dangerous, but also as the direct cause of its chief characteristics.

A very interesting clinical comparison of antipyretic power has been made by Pavay[2] upon a febrile patient suffering from phthisis. Using quinine, salicylate of sodium, and antipyrin, he found that the effects were identical if of quinine 15 to 22 grains, of antipyrin 37 grains, and of salicylate of sodium 45 grains were used.

In Ziemssen's *Archiv für klinische Medicin*, Sara Welt has recorded the results of the use of antipyrin in 122 cases, of whom 62 were males and 60 females. Of this number 88 suffered from enteric fever.

She found that doses of 30 grains secured complete effects in 72 cases 490 times, while a dose of 120 grains caused a complete apyrexia on one occasion at once, and 150 grains acted similarly in another patient,—a result not to be wondered at save that death did not occur as a result of the avalanche of drug.

In France, Laure[3] has tried the drug in the children's wards of the Charité de Lyon, and he concludes that antipyrin is far superior to quinine in all the febrile maladies of childhood, save malaria, and that it is particularly valuable in children. This opinion is also confirmed by Moncorvo,[4] of Brazil, but is vehemently opposed by Jacubowitsch, who asserts that, by reason of the decrease in urinary flow, the drug is dangerous in children.

[1] Deutsche Arch. für klin. Med., vol. iii, 1867.
[2] Wiener Medicin Wochenschrift, 1886, No. 8.
[3] Revue Mensuelle des Malades de l'Enfance, Feb., 1886.
[4] Berliner klin. Wochenschrift, April, 1887.

One of the best studies as to the value of antipyrin in children's ailments has been recorded by Argutinski,[1] who has used it in croupous pneumonia, the patients' ages being from 4 to 8 years. The drug was given in doses of from 7 to 15 grains every hour for two or three doses.

It was found that the fall of temperature usually began after the first dose, and fell rapidly during the first three hours, after which time it continued falling or remained stationary for twelve to eighteen hours more, and, if very large doses were used, the apyrexia lasted for forty-eight hours.

In 4 cases out of 5 no rise occurred in the temperature after the primary fall. The heart and circulation remained unaffected, except that the pulse became a little slower with the decrease of the fever. No exhaustion was produced by the drug, and the condition of the patients became more cheerful and bright.

In the *Prager Medicinische Wochenschrift*[2] Pribram published one of the earliest clinical reports that we possess of the value of antipyrin. From these studies he concluded that it acts when quinine fails, that it is as efficacious in acute rheumatism as salicylic acid, and that in phthisis it tends to prevent loss of bodily weight. In Schmidt's *Jahrbücher*[3] may be found several papers of a similar character.[4]

It is worthy of note that Ernst[5] was one of the first

[1] Vratsch, Nos. 41–42, 1884.

[2] Oct. 1, 15, 22, 1884

[3] Oct. 21, 1884, p. 127.

[4] The following is a list of the more important papers appearing at this time: Filehne, Zeitschrift für klin. Med., viii, 1884. Guttmann, Berliner klin. Wochenschrift, No. 20, 1884. Alexander, Breslauer Arztl. Zeitschrift, ii. Hofer, Wiener Med. Wochen., No. 47, 1884. Batak, Casopis ceskych lekarnv, Nos. 47–52, 1884.

[5] Bulletin Gén. de Thérapeutique, Oct. 30, 1884.

to notice the exanthematous rash which sometimes appears.

The important statement of Steell,[1] made in 1885, that typhus fever fails to respond to antipyrin as favorably as does typhoid fever, has been found true by others and is worthy of attention.

Antipyretic Influence.—Ever since Filehne[2] received from the hands of Ludwig Knorr, of Munich, the substance known as antipyrin, the drug has been used to check fever with almost certain results, and so generally recognized is this power that the writer will not stop to give a long array of evidence as to its existence. He will rather attempt to point out the conditions and circumstances which call for its use and under which it will most probably act advantageously or disadvantageously.

The question of vital importance which at once comes forward for decision is as to whether a drug which lowers a fever in any way shortens the duration of those diseases which run a given course, as typhoid fever, pneumonia, or any one of the affections which end in crisis or lysis.

While it is true that antipyrin may be employed in any disease associated with high temperature, such as typhoid fever, pneumonia, or erysipelas, it must not be forgotten that but one object is gained by its use. Antipyrin, even though its influence may be most favorable in a given case, still accomplishes nothing in the way of cure. Antipyrin only governs the heat processes while the disease plows its way onward to recovery or death; although it may, by quieting restlessness due to the fever or to the nervous disorder produced by the dis-

[1] Med. Chronicle, 1884–85, p. 497.

[2] Zeitshrift für klin. Med. Berlin, 1884, vii., p. 641.

ease, render the pathway to recovery more easy, but no shorter than if it were not employed.

Many physicians have looked and still look upon antipyretic treatment as curative in its effects, but nothing can be more distant from the truth. It should be distinctly understood and taught everywhere that these drugs belong to a peculiar class; a class of drugs to which we gladly turn when told "to treat the symptoms as they arise;" a class of drugs which are to be used solely for the relief of the symptoms of the disease, and not for the cure of the disease itself.

Typhoid Fever and Fever of Typhoid Type.—In the early part of this essay the writer said so much concerning the time at which antipyretic treatment is to be resorted to that it is unnecessary to repeat it here. In his opinion, antipyrin should play a secondary rôle in the reduction of the pyrexia of the typhoid state, our main reliance being upon cold applications, and the antipyrin only being used as an adjuvant to help the cold bath or packing. Aside from the fact that he has found such an opinion to be well based upon good results in a large number of typhoid-fever cases, this belief seems to be founded upon perfectly good logical therapeutic reasoning. Even if antipyrin were perfectly innocuous, its constant use in fever would but give the already overstrained kidneys the task of its excretion, while the stomach, sufficiently disturbed by necessary medicine and illness, has enough to do without an additional load. Further than this, we know that the drug is not perfectly harmless, and we also know that if it acts on the protoplasm of the body it must finally be given in larger and larger dose, lest it lose its power. This is not the case with the cold pack or application, which never loses its power through prolonged use.

The writer feels sure that antipyrin should be given in typhoid and other low fevers of a continued type only when the cold pack cannot be used, or at the end of the cold application to prevent the temperature from bounding upward after its depression.

Further than this, the fever will sometimes resist all doses of antipyrin that we can give, or, at any rate, all that it is safe to give. No fever can resist the cold bath.

In diseases of a more chronic type, more particularly those represented by phthisis, antipyrin is of doubtful value, owing to the increased sweating so apt to be produced by the drug, and, unless the patient seems to be particularly robust, it should not be employed except in the smallest available doses.

Sthenic Fevers.—The application of antipyrin to the febrile temperatures occurring in sthenic cases has an entirely different outlook and purpose than in the prolonged low fever of the adynamic type. There can be little doubt that in sudden, excessive outbursts of a febrile paroxysm in a child, without any acute disease underlying it, antipyrin is of great value, and there are also reasons for its employment in order to favor popular prejudice. In America, at least, a physican visiting a case of croupous pneumonia at its onset with a high fever would not be allowed to give the patient a cold bath, if the friends could prevent it, and must, in consequence, fall back upon antipyrin.

Again, the fever of such cases is not prolonged enough to necessitate the use of antipyrin day after day, for weeks at a time, and there is, therefore, less danger of the body being injured by its influence. In scarlet fever its use should be most carefully watched, for the double reason that the kidneys are in danger, and that the disease, accompanied by fever, may last a long

time. In pneumonia and erysipelas, in strong persons, antipyrin finds its true place. Lasting about a week in their febrile activity, these diseases are often accompanied by sudden hyperpyrexias, which must be overcome at once by a drug, and the fever is so apt to rise to a dangerous degree that some remedy has often to be left in the hands of the nurse, with instructions to use it if a hyperpyrexia should assert itself.

In thermic fever, or the hyperpyrexia of sun-stroke the employment of antipyrin is often useless. The excessively rapid upward dash of the temperature responds in no way to the drug, and there are cases on record in which its use has utterly failed of good result. Thus, in one case reported by Singer,[1] a man suffering from thermic fever with a temperature of 108.4° F. received 50 grains of antipyrin hypodermically at 6 P.M. At 7 P.M. he received 10 grains more under the skin, and at 8 P.M. 20 grains more. At 9.30 another 20 grains were used. In other words, 100 grains hypodermically in three and a half hours proved useless.

That the drug may do good if the temperature is not excessive is proved by many observations, and an interesting clinical report on the successful use of antipyrin in the sun-stroke of children, which was probably not true heat-stroke as we know it, has been published by Demme.[2]

It has been stated by some practitioners that antipyrin may produce serious cardiac weakness at the time the fall of temperature occurs, and these writers have pointed out that, though experimental studies show antipyrin in moderately large doses to be devoid of cardiac influence, clinical experience reaches opposite results.

[1] New York Medical Record, Dec. 25, 1886.
[2] Wiener Med. Presse, July 17, 1887.

This apparent contradiction between empiricism and science is, however, by no means real, as we will explain.

The studies of Lauder Brunton and others, already quoted by the author of this essay, have abundantly proved that the application of heat, not only to the heart of the frog but to that of the mammal, renders its movements much more rapid, and, to a certain point, more powerful, provided that the heart has not been weakened by some prolonged exhausting condition and is in such a state that scarcely any measures can be resorted to for its restoration. In this we see an explanation, in part, of the high, bounding, but rapid pulse of sthenic febrile conditions. It is a law that every muscular fibre always experiences a condition of more or less depression after unusual exertion, and this is particularly the case whenever the stimulation causing the increased exertion is suddenly withdrawn. If, therefore, the heart of a patient is stimulated by the heightened temperature of a fever for a day or two and is already beginning to be tired out, it is evident that a large dose of antipyrin may indirectly withdraw in a few minutes the only stimulus it has and produce a depressed condition of the cardiac muscle at a time when the general system, not depressed by the disease as yet, may be making as great calls for blood as before. The argument against this is, that if the fever by stimulating the heart will result in its exhaustion, the sooner the fever is reduced the better it is. This is partly true, and it is just between the points of too much drug and none at all that we must take our path, the idea being to relieve the fever slowly, not by one huge dose. This does not apply to those cases where the condition is one of hyperpyrexia and where the danger is immediate from involvement of the heart and higher nervous centres.

Malarial Disease.—In malarial disease antipyrin certainly exerts no antiperiodic influence, although it controls the febrile paroxysms to a very great extent; yet, while this is the opinion of the majority of those who have used it, it cannot be said that every observer has reached similar conclusions. Thus, we find Potter [1] reporting cases where the results obtained were most satisfactory when large doses of antipyrin, frequently repeated, were used. He obtained particularly good results from its use in the remittent type of malarial poisoning, and found it to succeed when the other measures usually employed had failed.

One cannot help thinking that, in many of the cases where antipyrin has been reported as acting as an antiperiodic, it has simply lowered the fever, and so seemed to favorably affect the disease. Such an instance is recognized and mentioned in one of the recent German journals.[2]

Nervous Diseases, Particularly those Associated with Pain.—Almost as soon as it was discovered that antipyrin possessed antipyretic powers, it was known that it could also relieve pain, and, although this feature of its action was not fully recognized on all sides until the papers of Lepine[3] and Sée[4] were published, it had nevertheless been recorded previously by Alexander,[5] Demme,[6] Demuth,[7] Masius,[8] Lenhartz,[9] Bernheim,[10]

[1] Lancet, London, April 10, 1886.
[2] Deutsche Med. Zeitschrift, 1887.
[3] Centralblatt für die Gesammte Therap., Jan., 1887.
[4] L'Union Médicale, April 26, 1887.
[5] Centralblatt für klin. Med., No. 33, 1884.
[6] Fortschritte der Medicin, No. 24, 1884.
[7] Aertzliches Intelligenzblatt, Dec., 1884.
[8] Bulletin de l'acad. Royale Méd. de Belgique, No. 1, 1885.
[9] Chariten Annalen, Bd. x, 1885.
[10] Revue Médicale de l'Est, April 15, 1885.

Neumann,[1] Blanchard,[2] Moncorvo,[3] Fraenkel,[4] and Clement.[5] All of these clinicians had, however, only found it useful in rheumatic and gouty pains, and it was rather supposed that the relief was due to an action on the disease than to any analgesic properties of the drug.

The use of antipyrin for the relief of other pains than those just named, was undoubtedly first carried out by Khomiakoff and Livoff[6] in migraine, and by White[7] and Sprimont[8] in hemicrania, a virtually identical neurosis. These results have been confirmed by Ogilvey,[9] Kingsbury,[10] Berdach,[11] Wright,[12] Guardia,[13] Suckling,[14] Dujardin-Beaumetz,[15] Ungar,[16] Martin, and an infinite number of others.

By far the most important of these studies are those of Germain Sée,[17] and so similar are the results of the every-day use of antipyrin at present to the observations of this writer that it is unnecessary to do more than give his conclusions, which sum up our knowledge, particularly if we include his second contribution[18] on the subject. He found that the drug relieved in an extraordinary degree the agony of gout and of rheumatism and

[1] Berliner klin. Wochenschrift, Sept. 14, 1885.
[2] Revue Med. de la Suisse Romande, May, 1886.
[3] Paris Thesis, 1886.
[4] Berliner Med. Gesellschaft, Oct. 18, 1886.
[5] Lyon Méd., Aug. 29, 1886.
[6] Vratsch, No. 5, 1885, p. 867.
[7] New York Medical Record, Sept. 11, 1886.
[8] Med. Obozren, No. 23, 1886.
[9] British Med. Journal, Jan. 14, 1888. [10] *Ibid.*, Dec. 24, 1887.
[11] Wiener Med. Wochenschrift, March 10, 1888.
[12] Practice, Jan., 1888.
[13] Rivista de Ciencias Medicas Barcelona, Feb. 20, 1888.
[14] British Med. Journal, June 11, 1887.
[15] Therapeutic Gazette, Oct., 1887.
[16] Centralblatt für die Gesammte Therap., Jan., 1887.
[17] L'Union Méd., April 26, 1887.
[18] *Ibid.*, Sept. 10-13, 1887.

other forms of pain associated with diathetic states. More important than all, however, he recorded a large number of instances where the drug alleviated headache, facial neuralgia, and obstinate migraine with rapidity and completeness. He found antipyrin of value in the pains of neuritis and tabes dorsalis, and his assertion that it surpasses opium in giving relief in the crises of the latter disease has received confirmation the world over.

In the contribution made some time later (*loc. cit.*), Sée recorded the relief obtained in cases of abdominal pain associated with visceral disturbances, such as renal and hepatic colic, colic of the gastro-intestinal type, and that associated with the uterus. He also praises the power of the drug in angina pectoris in all its forms, and the writer of this essay has also used it successfully in this disease.

Almost synchronously with the appearance of this paper by Sée, one by Seifert,[1] of Würzburg, of a similar type was published, and the German writer not only supported the earlier author, but also recorded the value of antipyrin in chorea,—a report which has been highly indorsed by H. C. Wood[2] more recently in this country.

Fraenkel, to test the correctness of the views of Sée, almost immediately took morphine away from his patients and substituted antipyrin in its stead, with the most encouraging results, and he further proved that the action of about 5 grains of antipyrin was equal to $\frac{1}{20}$ grain of morphine.

Even if it were possible, it would be out of place for the writer to give any further quotations from the literature of this subject, and what has been said has been

[1] Centralblatt für klin Med., No. 35, 1887.
[2] Therapeutics, Phila., 1888.

mentioned rather as an evidence of the diverse actions of the drug than with the idea of giving a thorough review of the general and wide-spread power of antipyrin for the relief of pain.

ANTIFEBRIN.

Experimental Evidence.

Although brought to the physician as a remedy quite two years after its fellow, antipyrin, antifebrin has undergone an amount of study which only an epoch marked by a yearning after a good febrifuge could bring forth. Further than this, the clinical and physiological studies made upon it in many ways seem more to the point and more thorough than those on antipyrin, perhaps because the examination of the effects of that drug had taught us what to look for. On the other hand, the partial insolubility of the drug renders physiological studies concerning it far more difficult of completion.

Heat Functions.—Following out with antifebrin the course already pursued with antipyrin, let us attempt to discover what its influence is upon the temperature of the normal animal.

In the spring of 1887, the writer[1] and Evans[2] carried out a series of investigations as to the general effects of antifebrin, and paid especial attention to the question now before us. The writer found in rabbits, free to run about, that a very distinct fall, often exceeding 1° F., in the normal bodily heat took place, and he also obtained a similar result with dogs attached to the manometer and in the calorimeter. His results were confirmed by Evans, who used rabbits in a calorimeter. On the other hand, Cahn and Hepp[3] did not find that antifebrin constantly produced a fall in the normal animal, but that it did do so in the majority of instances. The following

[1] Therapeutic Gazette, June, 1887.

[2] Centralblatt für klin. Med., 1886, vii, p. 561.

[3] *Ibid.*

experiments, made more recently by the writer, are of interest in this connection, as they tend to support the earlier statements already published :—

Experiment No. 1.—Rabbit; weight, 3 lbs.; full grown; doe.

	Rectal temperature, ...	102.1
1.13	Gave hypodermically 2 grains of antifebrin.	
1.20	Rectal temperature, ...	102.1
1.30	" "	102.
1.40	" "	101.4
1.50	" "	101.2
2.	" "	101.
2.30	" "	101.2
3.	" "	102.

Experiment No. 2.—Rabbit; weight, $2\frac{1}{4}$ lbs.; full grown; buck.

1.25	Rectal temperature, ...	103.
1.28	Gave hypodermically into the side 2 grains of antifebrin.	
1.35	Rectal temperature, ...	102.9
1.40	" "	103.
1.50	" "	102.7
2.	" "	102.6
2.10	" "	102.3
2.20	" "	102.1
2.30	" "	101.8
2.40	" "	102.1
2.50	" "	102.3

Experiment No. 3.—Rabbit; weight, $2\frac{3}{4}$ lbs.; black; full-grown; doe.

3.10.	Rectal temperature, ...	102.6
3.13.	Gave 2 grains of antifebrin as before.	
3.25.	Rectal temperature, ...	102.7
3.35.	" "	102.6
3.45.	" "	102.3
3.55.	" "	102.1
4.05.	" "	101.7
4.15.	" "	101.4

That antifebrin lowers fever temperatures with great rapidity and thoroughness is so well attested by clinical observation as to make any examples of such an action unnecessary, for, if any is required, it can be found scattered everywhere through the literature of medicine for several years and is included in the clinical consideration of the drug which follows this portion of this paper.

It having been decided that antifebrin lowers normal heat, it remains to be discovered how this lowering takes place, and the experiments of the writer and Evans would appear to decide this point. Evans asserts that in 9 animals he found an increase in heat dissipation in 7 cases, with a decrease in heat dissipation in the remaining 2. In 5 of the 9 heat production was decreased and in 4 increased. In the studies made by the writer on 5 dogs he found production decreased in 4 cases and increased in 1. It would appear, therefore, that the fall is due to decreased heat production and increased heat dissipation, as a general rule.

On the fevered animal, antifebrin acts by decreasing heat production and dissipation, according to the studies of both the writer and Evans; and, as the decrease in dissipation is not so great as is that of production, it is probable that it simply follows the lessened production, or, in other words, less heat being produced, less is eliminated.

It has been stated by Wood that the researches of the writer and of Evans are here at fault, in that the temperature did not fall under the doses employed by them. This is certainly untrue of some of the experiments of Evans and of some of those of the writer, as examination of their papers will show. Thus, in experiments No. 2, No. 3, and No. 5 of Evans, a fall of temperature did occur, with the changes in heat mechanism

already named; and in those of the author, Nos. 17, 18, and 19 also showed a fall with the same changes in the heat functions. It would seem, therefore, that their conclusions, as based on these experiments, are worthy of acceptance.

Bokai[1] has also asserted that the power of antifebrin in reducing temperature, when given in medicinal quantities, depends upon its power of lessening heat production. His basis for this is one which is partly hypothetical and partly founded on experimental proof, namely, that as the drug paralyzes the peripheral motor nerves, in poisonous doses, so does it also depress them when in medicinal amount, and thereby prevents heat changes in the muscles.

This theory is one which it is impossible for the writer to consider, simply because we have no right to suppose that the muscles are our chief source of heat; nor have we as yet complete proof that paralysis of the motor nerves lowers heat production. Lastly, we are without evidence, even if these nerves contain trophic or heat fibres, that antifebrin paralyzes any fibres but those intimately associated with movement and not with nutrition.

If a toxic dose is used, Bokai thinks that vascular dilatation is an important factor in the fall of temperature and dissipation of heat.

Circulation.—As the influence upon the circulation of any substance used as a drug must or ought to be known before it is generally employed, this portion of our study is most important.

Dividing the circulatory effects into those changes produced by toxic and medicinal amounts, let us first consider the former.

[1] Deutsche Med. Wochenschrift, Oct. 20, 1887.

When antifebrin is applied to the isolated frog's heart, Lepine[1] states that it beats more rapidly and strongly, but soon becomes weakened if the amount of the drug be large, the viscus finally ceasing to beat in wide diastole. The same result, so far as cardiac arrest is concerned, has been reached by Herczel,[2] experimenting on the rabbit, and Weill[3] has also noted that the heart of the frog, while at first stimulated, is ultimately depressed by large amounts. The writer has confirmed these results, and has also found that, when antifebrin in large amounts is injected into the jugular vein of a dog, it produces at once a fall in arterial pressure, with a diminution of the size of the pulse-waves, and all the general evidences of cardiac and circulatory depression, notwithstanding the fact that, as death occurs from respiratory failure, asphyxia is present. (See tracing No. 1). The cause of this fall seems to be due to a direct depressing action on the heart, associated with failure of the vasomotor system, as asphyxia causes no rise in arterial pressure.

Turning to a consideration of the influence of antifebrin upon the circulatory system in ordinary medicinal amount, we find that it either has no influence, if the quantity of the drug be quite small, or else, if it be large enough to produce any change, we have a condition which does not seem to be dependent so much upon a dominant action of the drug as the state of the animal at that time. Thus, in the experiments detailed by Evans,[4] he found virtually no changes in pressure and pulse-rate in two experiments in which he gave from .015 gramme to .03 gramme, while in a third the arterial

[1] Compt. rendus de la Soc. de Biolog., July 1, 1887.
[2] Centralblatt für die Medicin. Wissenschaften, No. 30, 1887.
[3] Bull. Générale de Thérapeutique, Feb. 28, 1887.
[4] Therapeutic Gazette, 1887.

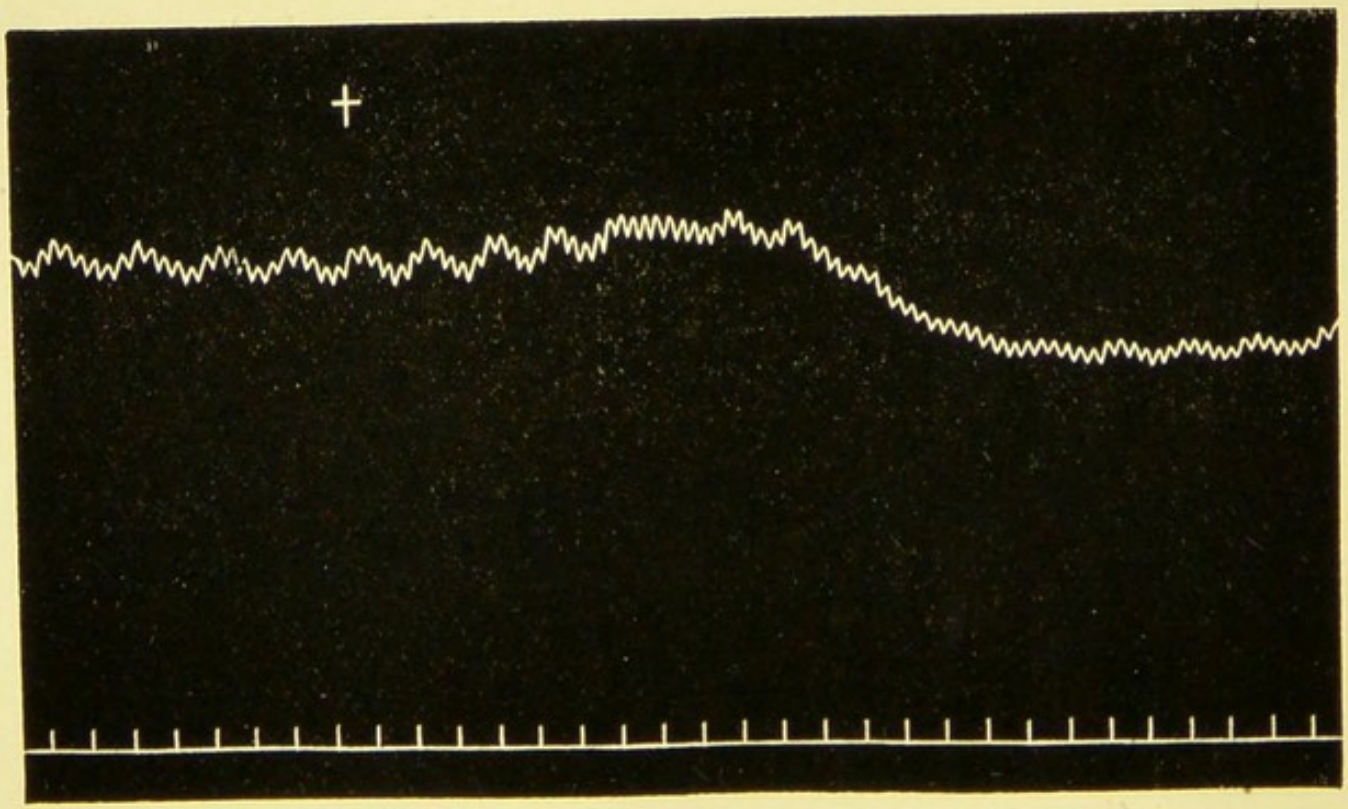
pressure was slightly raised. The writer has also found and stated, in an earlier paper, that the circulatory influence of antifebrin was very inconstant, and that the pressure and pulse are sometimes increased, sometimes decreased. More recently he has made other experiments, an example of which follows, in regard to this matter, and has reached results confirmatory of his earlier investigations. (See tracing No. 2.)

In the article on antipyrin it was shown that there was no relation between arterial pressure, pulse-rate, and the fall of temperature under the influence of that drug, and the same facts exist in regard to antifebrin. Although the pressure in the normal animal tends to fall with the temperature, it must be remembered that with antifebrin, which is itself depressant to a slight extent, a very great fall should ensue if the fall of bodily heat depended in any way on the vascular changes produced by the drug. The charts published by the writer [1] in 1887 show this very well.

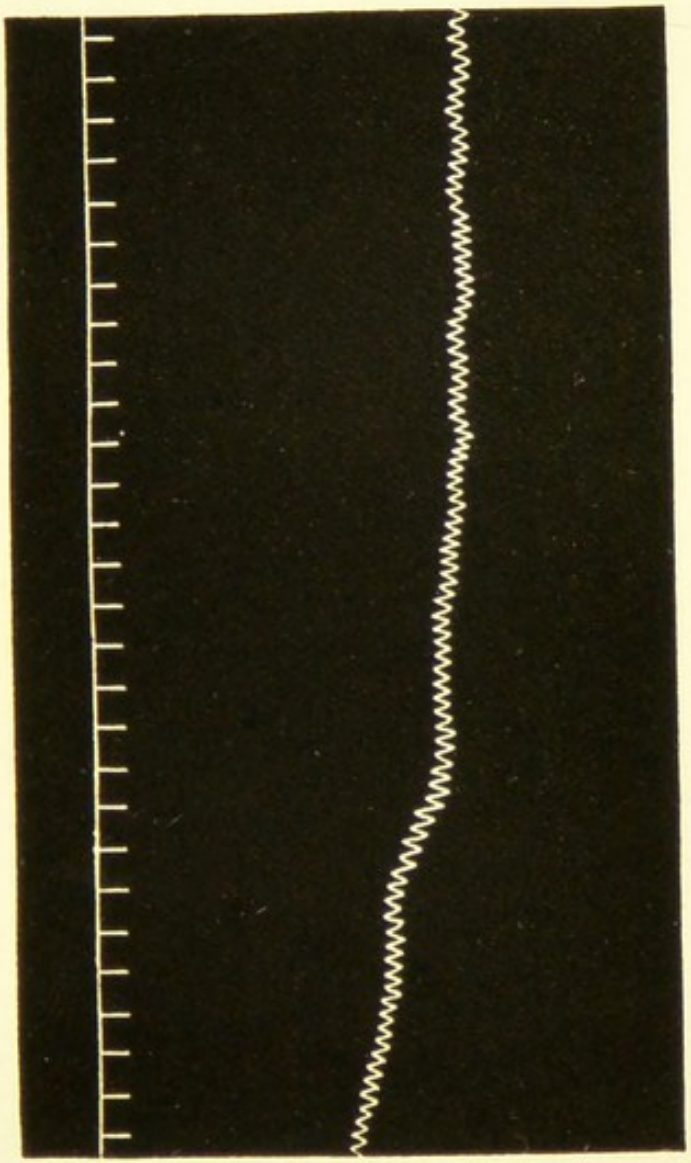
On the fevered animal there seems to be no relationship between blood-pressure and bodily temperature, although the influence of the drug over the fever produced by the use of pepsin is not very powerful. At the same time the results reached confirm those made upon the normal animal in regard to this point and agree perfectly with the experiments of other investigators.

Blood.—From a toxicological and physiological point of view, antifebrin exerts, when given in large doses, more influence on the blood than upon any other part of the body. Added to freshly-drawn blood or to the blood in the body, it produces a peculiar change in the color, the normal red becoming brownish. Abundant

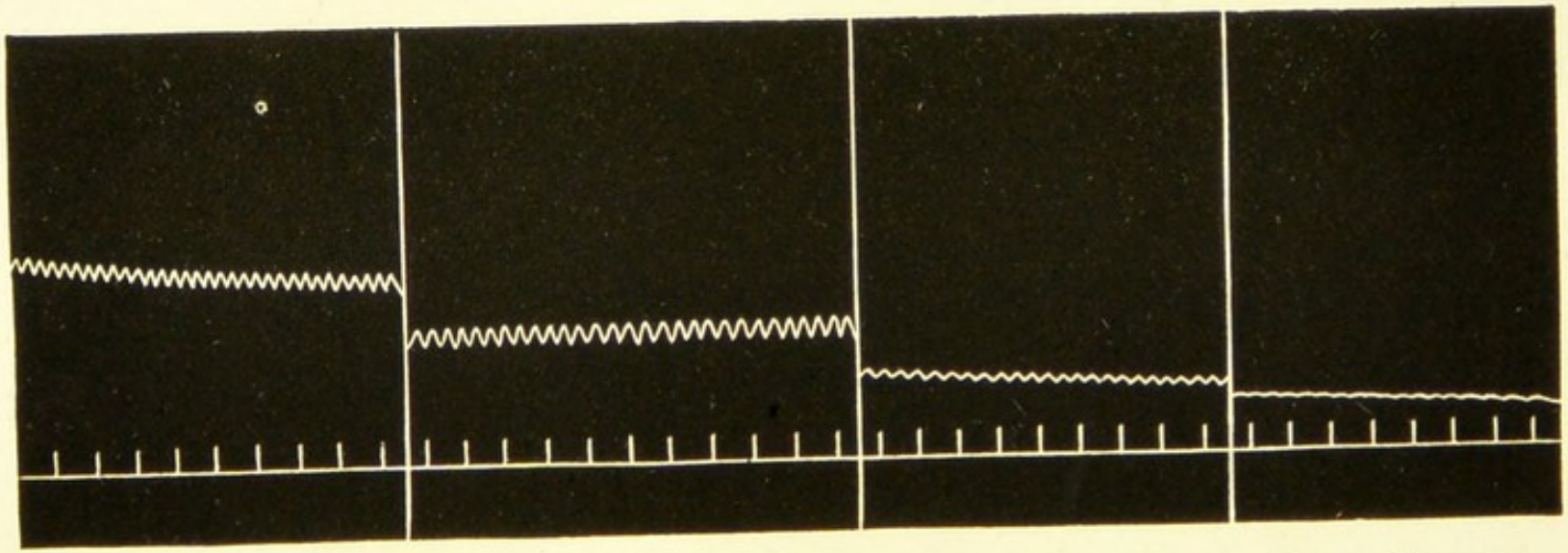
[1] Therapeutic Gazette.



TRACING No. 1.—DOG; WEIGHT, 16½ POUNDS. VERY LARGE DOSE, 1 GRAIN TO THE POUND, INJECTED INTO JUGULAR BETWEEN + MARKS.



SAME CONTINUED.

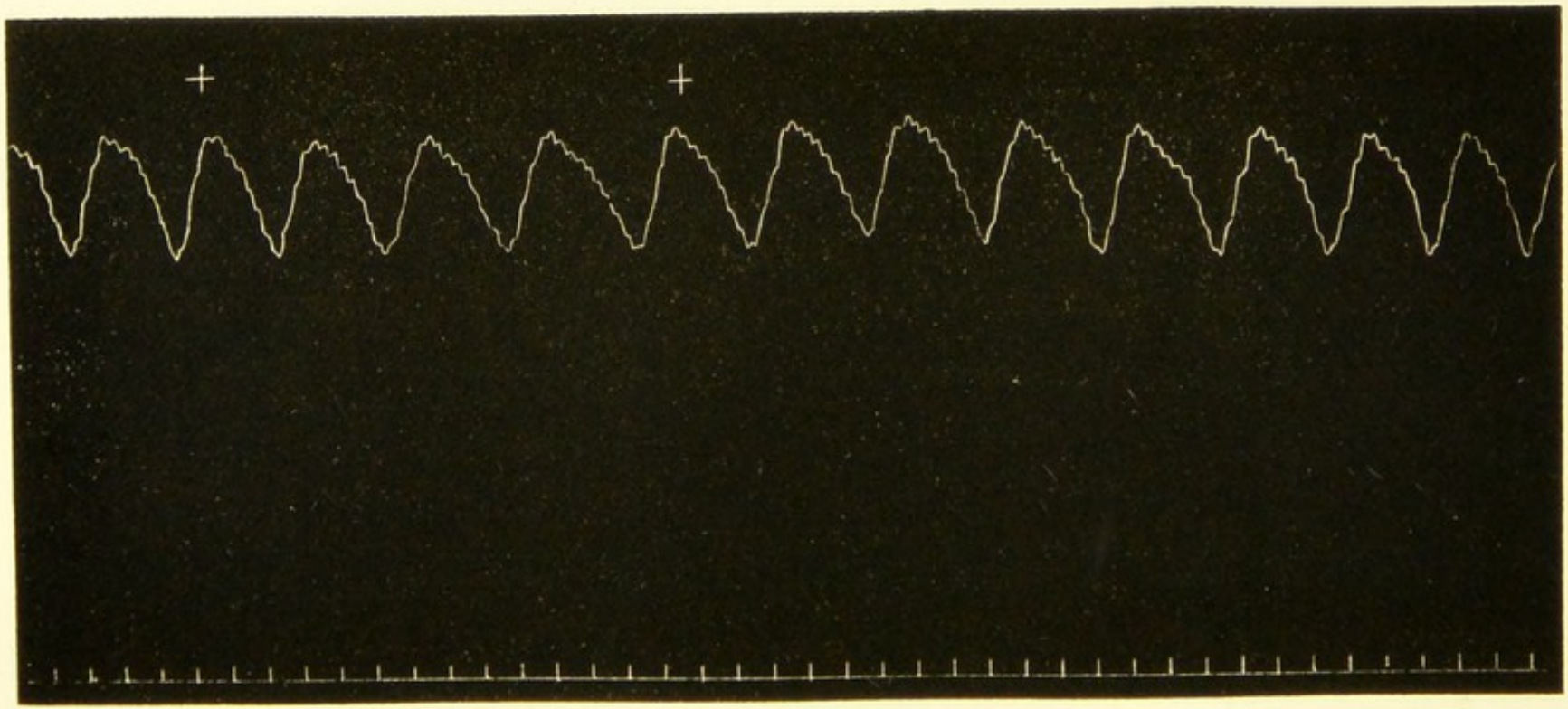


SAME, ONE MINUTE LATER.

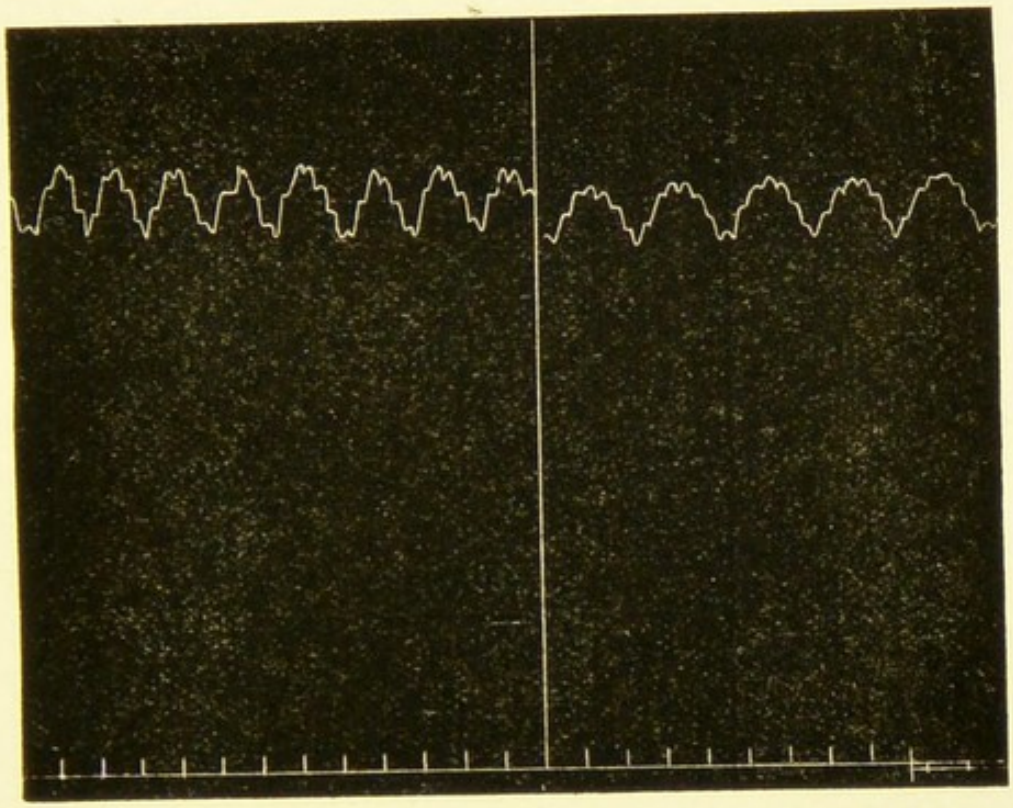
ONE MINUTE; VAGI CUT: NO RESULT.

TWO MINUTES LATER.

THREE MINUTES LATER; DYING.



TRACING No. 2.—DOG; WEIGHT, 9 POUNDS. SHOWING EFFECT OF SMALL DOSE, 1½ GRAINS, INJECTED INTO JUGULAR BETWEEN + MARKS.



SAME CONTINUED, TWO MINUTES LATER.

SAME CONTINUED, THREE MINUTES LATER.

investigation on the part of Weill,[1] Henocque,[2] Herczell,[3] Müller,[4] Bokai,[5] and Evans[6] has proved that toxic doses decrease not only the oxidizing power of the blood, but also produce in it the changes which give the spectrum bands of methæmoglobin.

While unanimity exists as to the changes in color in the blood, no such coincidence is present in regard to the number and character of the blood-corpuscles under the influence of antifebrin. Lepine and Aubert (*loc. cit.*) claim that the corpuscles are reduced in number, but that their form remains unchanged; while Herczell reports that they will no longer form rouleaux, but are granular, thinned, and non-coherent. Directly opposing himself to Lepine, he finds no numerical decrease. Herczell is, however, in accord with the French investigators in the statement that free coloring matter is set free in the blood. If this is the case there must be some loss of corpuscles in this dissolution, and all observers are in accord in the belief that the persistent use of antifebrin may so alter the blood as to produce death. (See "Toxic Action," p. 72.)

The quantity of hæmoglobin reduced by antifebrin is very considerable. Henocque states that 6.5 per cent. of all the hæmoglobin of the blood must be so altered before the spectroscope shows the methæmoglobin band. When it is remembered that the normal reduction of the oxyhæmoglobin in the veins only equals 5 per cent., it is at once seen that the arterial blood under such circumstances is less able to perform its function than is venous blood ordinarily.

[1] Bulletin Gén. de Thérap., Feb. 28, 1887.
[2] Compt. Rendus Soc. de Biol., Paris, 1887–88, iv, 498.
[3] Wien. Med. Wochenschrift, 1887, 1021, 1057, 1085, xxxvii.
[4] Gazette Méd. de Strasburg, 1886, xv, 128.
[5] Pest. Med. Chir. Presse, Budapest, 1887, xxiii, 469.
[6] Therapeutic Gazette, 1887.

According to Herczell, the alkalinity of the blood is decreased, the urine becomes dark and brownish in color, and the blood-crystals of Teichmann can be obtained from it. The research of Herczell is of value in that it also shows us how nearly related antifebrin is to aniline.

Tissue Waste and Urine.—A great deal of contradictory evidence in regard to the influence of antifebrin upon tissue waste or metabolism and urinary flow has been given us by various investigators, chief among whom may be named Lepine,[1] Bokai,[2] Pasternatski,[3] Cahn and Hepp,[4] the first clinicians to employ it, Lang[5] and Solaro.[6]

Lepine found, in a very careful series of studies, that there is produced by antifebrin an augmentation in the excretion of urea and uric acid. Unfortunately, however, Lepine's conclusions are opposed to the results obtained by others. Bokai believes the nitrogenous elements of the urine are decreased and that it is by this means (decreased tissue change) that antifebrin lowers fever. Pasternatski also reaches similar conclusions, but it is only just to say that the researches of Lepine surpass, in the care exercised in their performance, those of his opponents.

In a series of studies carried out by Taylor,[7] under the direction of Chittenden, results were reached which support those of Lepine. This observer placed a young man, about 62 kilos in weight, under a condition of nitrogenous equipoise, and then examined the urine for ten days, when antifebrin was given, and during a

[1] Lyon Médicale, April 24, 1887.
[2] Deutsche Med. Wochenschrift, Oct. 20, 1887.
[3] Vratsch, Nos. 2 and 4, 1887.
[4] Deutsche Med. Wochenschrift, No. 16, 1887.
[5] Wiener Medicin. Wochenschrift, May 29, 1887.
[6] Medica Contemporanea, 1887.
[7] Studies from Labor. Phys. Chemistry, Yale, vol. iii.

second period of ten days, when antifebrin was again employed. The dose used was a little over 6 grains a day at the first, and this was rapidly increased to 40 grains a day, given in three doses.

As a result of these studies, Taylor believes that antifebrin slightly increases the excretion of urea, while the amount of sulphur remains almost unchanged. It was also found that the excretion of phosphorus was unaffected by the drug.

In the studies on the excretion of uric acid, however, the results reached indicate a distinct inhibitory action on the part of antifebrin. Berezooski finds, very naturally, that the quantity of urea decreases with the fall in temperature.

According to the remarkably careful and accurate studies of Muneo Kumagawa,[1] antifebrin produces, in the dose of 30 or 45 grains daily, no obvious alteration in the elimination of nitrogen in the dog; but if as much as 60 to 75 grains a day are employed, then a very considerable increase in nitrogenous elimination takes place, the mean increase being 30.8 to 35.7 per cent. It was also found that the increased elimination of 46 grammes of nitrogen during the administration of antifebrin (corresponding to 1353 grammes of meat or animal tissue) was exactly equalled by the decreased elimination of a similar amount during the twenty-five succeeding days. In forty-nine days of observation, during which very considerable loss of organic nitrogen and restitution of the same took place, no marked deficiency of nitrogen was observed. When considerable loss of nitrogen occurred, the sulphates followed irregularly.

Upon the quantity of urinary flow very great differ-

[1] London Med. Record, Oct. 20, 1888.

ences in reports exist. Weill[1] reports that he found it greatly decreased in amount, but that sometimes no change occurred. He never found the quantity of urine increased, while, on the other hand, Cahn and Hepp,[2] Solaro,[3] and Faust[4] assert that the urine is greatly increased in amount,—a conclusion which has been confirmed by Osler[5] in this country. The evidence seems to be so generally in favor of increased diuresis that for the present we must accept the latter conclusion as correct. The writer cannot help thinking that accurate measurements of the quantity of water and food ingested would show that the drug, in reality, has very little influence over the quantity of urine excreted unless extraneous factors are at work.

Nervous System.—The influence of antifebrin upon the nervous system is very marked indeed, the sensory portion of the nerves and cord being greatly quieted.

From the studies of Lepine[6] and Sardina[7] we obtain our chief knowledge of these facts, as well as from the researches of Herczell.[8] These investigators have found that large doses of antifebrin produce great quietude and a general anæsthesia, followed by total loss of all reflexes, and finally both motor and sensory paralysis. The portions of the nervous system involved are primarily the sensory side of the spinal cord and the sensory nerves, the motor side of the cord and the

[1] Bulletin Générale de Thérapeutique, 1886; also Thèse de Paris, 1887.

[2] Deutsche Med. Wochenscrift, No. 16, 1886.

[3] Rivista Medica Contemporanea, 1887.

[4] London Medical Record, July 15, 1887.

[5] Therapeutic Gazette, 1887, p. 165.

[6] Lyon Médicale, Oct. 31, 1886, and Semaine Médicale, 1886, p. 473.

[7] Contribution to the Physiological and Therapeutical Effects of Acetanilide on the Nervous System, 1887.

[8] Centralblatt für die Medicin. Wissenschaften, No. 30, 1887.

nerves being affected late in the poisoning or not at all. The drug in toxic doses does not affect the muscles, as has been proved by Bokai,[1] who finds a ready response made by them on the application of electricity; but he also finds that a similar application to the motor nerves is absolutely without effect, the muscles failing to respond, proving, Bokai thinks, that the nerves must be paralyzed peripherally.

Respiration.—The influence of antifebrin on respiration in ordinary doses is very slight; but if sufficiently large doses are used to produce very distinct physiological or toxic effects, this vital function is at once altered and impaired.

The writer also found that if as much as 1 grain to the pound of the animal be injected into the jugular vein death occurs at once, not from cardiac but from respiratory failure, the heart beating for some minutes afterward. If the dose be smaller, these effects are less severe but well marked, the respiratory movements being superficial and frequent, then irregular, arhythmical, then noisy, then quiet. That there are several factors in the production of these respiratory disturbances seems positive. Primarily there can be no doubt but that the early alterations in the character of the blood so influence oxygenation as to goad the respiratory centre to greater effort, while at the same time the centre is beginning to be directly depressed by the drug itself. Further than this, if Bokai's[2] assertion be true, namely, that the peripheral motor nerves are paralyzed, then a third cause of respiratory failure comes forward as a factor in the changes named.

Toxic Changes Produced by Prolonged Use.—Although it has been claimed by a number of clinicians

[1] Deutsche Med. Wochenschrift, Oct. 20, 1887. [2] *Ibid.*, Sept. 2, 1887.

that no untoward effects are produced by antifebrin when it is taken continuously for a long time, there can be no doubt that this is untrue. The changes brought about when a single large dose is given are too positive to allow of any other conclusion, even if we had no other evidence at hand. Very recently, however, Pisemski[1] has determined this point for us, to a certain extent, although his doses were very large. He found that when antifebrin was given by the stomach to four dogs in the daily dose of 2.5 grammes (37 grains), the animals died on the twelfth, fifteenth, sixteenth, and twentieth days, respectively, and the post-mortem examination revealed some congestion of the liver and brain, although the former organ was once or twice found to be very anæmic. The spleen was sometimes shrunken, sometimes normal, but the kidneys were always congested. A peculiar feature of this slow poisoning was the dark, voluminous clots found in the cardiac cavities.

Pisemski also noted a progressive diminution in the number of the blood-corpuscles from the beginning to the end of the tests.

Elimination.—During the first few months in which antifebrin was used by the profession it was stated that the drug was utterly destroyed in the body, being entirely consumed, but we now know that this statement is untrue and that such a belief arose simply from ignorance of the alterations it is capable of undergoing. Müller[2] is one of those who makes this statement. In a series of experiments carried out by Pavai-Vajna[3] it was discovered that antifebrin is eliminated as is ordinary aniline, namely, as para amido-phenol sulphate,

[1] Inaugural Dissertation, St. Petersburg, 1887, p. 48.
[2] Deutsche Med. Wochenschrift, 1887, No. 2.
[3] Centralblatt für die Gesammte Therapie, August, 1887.

and this observer has been confirmed by Matuzorszki,[1] who has found this compound present in the urine even when very small medicinal doses are employed. Jaffa[2] and Hilbert have confirmed these conclusions.

As a result of these studies it at once becomes evident that when antifebrin enters the blood it is broken up into acetic acid and aniline, and that this aniline is then changed into para-amido-phenol, which unites with the sulphuric acid in the body to form a sulphate.

This belief is still further substantiated by the physiological action of the drug, which is very closely allied to that of aniline, as has been shown by Herczel and others.

Cahn and Hepp, however, state that antifebrin escapes from the body unaltered, only a small amount undergoing any change.

Closely allied to this is the result reached by Wendriner,[3] who asserts that if a small quantity of antifebrin be added to normal urine and the fluid be made strongly alkaline with caustic soda and distilled, aniline will be found in the distillate. While this is true, he asserts that the urine of patients taking antifebrin as a medicine gives no such reaction for aniline, although the drug is undoubtedly decomposed in the body. The reason of this has been just pointed out, and the results of Pavai-Vajna and Matuzorski are supported by the further statement of Wendriner that the amount of phenol in the urine is increased. Wendriner states that the amount of phenol present is about $5\frac{1}{2}$ per cent. of the antifebrin taken.

Kumagawa[4] also asserts that neither antifebrin nor

[1] Endietol Orvoss-term. tud. Ersesito. Kolozsvar, 1887, p. 17.
[2] Zeitschrift für physiologische Chemie, 12, p. 307.
[3] Centralblatt für die Med. Wissenschaft, No. 8, 1887.
[4] London Medical Recorder, Oct. 20, 1888.

aniline are to be found in the urine after the drug has been taken, and indorses the statement of Pavai-Vajna as to the change into para-amido-phenol sulphate. This same investigator found that when given internally antifebrin is rapidly absorbed, even in large dose, and in the course of twenty-four hours completely eliminated by the kidneys.

Antiseptic Action.—According to Bokai[1] and Krieger,[2] antifebrin possesses decided antiseptic power, but their assertions are vehemently opposed by others, and are probably only partly correct. Lepine[3] strongly denies this influence, and he is supported by Dujardin-Beaumetz and by Miguel, the director of the micrographic service at the Meteorological Observatory of Montsouris.

Bokai noted that a 5-per-cent. solution was fatal to infusoria, to spirilla and bacilli, as did also Krieger.

There can be little doubt but that in excessive amount the drug has some slight power of this character, but nothing of sufficient note to be of use in practical medicine, and Cahn and Hepp[4] think that its powers in this direction are weak.

According to the assertions of Kumagawa,[5] the drug exercises a powerful antiseptic effect in catarrh of the bladder and upon the contents of the intestines.

Van Seer[6] has observed that milk does not become sour if saturated with antifebrin, and that albumen under such circumstances does not become putrid.

Conclusions as to the Physiological Action of Antifebrin.—1. Antifebrin lowers normal bodily temperature slightly.

[1] Deutsche Med. Wochenschrift, Oct. 30, 1887.
[2] Centralblatt für klin. Med., No. 44, 1886.
[3] *Loc. cit.*
[4] *Loc. cit.*
[5] *Loc. cit.*
[6] Virchow's Archiv, Bd. cxiii, p. 184.

2. Antifebrin lowers febrile temperature very rapidly.

3. The fall of temperature in the normal animal is due to decreased heat production and increased heat dissipation, as a general rule.

4. The fall of temperature in the fevered animal is due to decreased production and increased dissipation of heat.

5. Applied directly to the heart, antifebrin stops this viscus in diastole.

6. Although the drug may be apparently a cardiac stimulant, its dominant action is that of a depressant.

7. It causes a decrease in pulse force and rate and a fall in arterial pressure.

8. Antifebrin acts in toxic dose on the blood, changing the hæmoglobin into methæmoglobin.

9. On the urinary flow the drug has little effect; if any influence is felt the amount of urine is increased.

Antifebrin would seem to increase tissue waste, but this is doubtful.

10. Antifebrin depresses the spinal cord and motor and sensory nerves, but not the muscles.

11. When toxic doses are used death is due to respiratory failure.

12. Organic changes are produced by its prolonged use.

13. Antifebrin is eliminated as para-amido-phenol sulphate.

14. Its antiseptic powers are feeble.

Clinical Evidence.

When antifebrin is given in moderate medicinal amount to a healthy adult man, it produces, as a rule, no appreciable effect; but if the amount of the drug is

somewhat increased, somnolence, constipation, occasional headache and nausea, with malaise and a peculiar dusky, cyanotic appearance, come on.

In fevered individuals the symptoms may be much the same, save that frequently a great fall occurs in their temperature, which in some instances approaches collapse.

Although these signs generally come on only when large medicinal amounts are given, they nevertheless assert themselves in persons who have an idiosyncrasy to the drug, and for this reason the untoward effects are worthy of note.

In view of these facts the writer has collected a number of such instances, and has tabulated them in the following pages. From these it will be seen that the most frequent untoward effect was collapse with symptoms of depression, accompanied by cyanosis and rigors.

The age and sex in which such symptoms showed themselves may be tabulated as follows:—

Males.	*Females.*
1 to 10 years, 2 cases.	1 to 10 years, 1 case.
10 to 20 " 8 cases.	10 to 20 " 3 cases.
20 to 30 " 4 cases.	20 to 30 " 5 cases.
30 to 40 " 3 cases.	30 to 40 " 4 cases.
40 to 50 " no case.	40 to 50 " no case.
50 to 60 " no case.	50 to 60 " 1 case.
60 to 70 " no case.	60 to 70 " no case.
70 to 80 " no case.	70 to 80 " no case.

A large number of the reported cases did not have the name and sex given in the original report.

The dose, as will be seen, was generally a moderate one, from 3 to 10 grains, although rarely it was much larger.

UNTOWARD EFFECTS OF ANTIFEBRIN, No. 1.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Tempera-ment.	Disease.	Remarks.
Not stated.	Not stated.	15 grs. at a dose for 8 doses.	Sudden.	Collapse and death; coldness and rigidity.	Very short.	Death.	Hardy, La Sem. Méd., Feb. 22, '88; also, Brit. Med. Jour., Mar. 24, '88.	Not stated.	Not stated.	
18	M.	3 grs. at one dose for 8 doses in 4 dys.	At once.	Collapse; profuse sweat; cyanosis of face.	A few hours.	Recovery.	Kronecker. Therap. Monatshefte, September, 1888.	Not stated.	Typhoid fever.	
25	F.	3 grs. in one dose.	At once.	Slow fall of temperature, followed by a rigor.	Short.	Recovery.	Kronecker. Therap. Monatshefte, September, 1888.	Not stated.	Typhoid fever.	
11	M.	15 grs. in one dose.	At once.	Nausea and profuse diarrhœa.	Short.	Recovery.	Demme. Intern. klin. Rundsch., No. 4, 1888.	Not stated.	Phthisis.	
Child.	Not stated.			Nausea and profuse diarrhœa; cyanosis.	Short.	Recovery.	Demme. Intern. klin. Rundsch., No. 4, 1888.	Not stated.	Phthisis.	
1	M.	2 grs. at once.	At once.	Dangerous collapse.	A few hours.	Recovery.	Löwenthal. Therap. Monatshefte, September, 1888.	Not stated.	Pneumonia.	
Not stated.	Not stated.	5 grs. in one dose.		Great prostration.	A few hours.	Recovery.	Kiernan. Medical World, October, 1888.	Not stated.	Typhoid fever.	
	Not stated.			Profuse sweat; depressed heart; cold extremities.		Recovery.	Bringier. Medical World, October, 1888.	Not stated.	Typhoid fever.	

UNTOWARD EFFECTS OF ANTIFEBRIN, No. 2.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Tempera-ment.	Disease.	Remarks.
4		4 grs. in one dose.	In 1 hour.	Alarming collapse, with very low temperature.	Short.	Recovery.	Saylor. Times and Register, 1889.	Not stated.	Fever.	
15	F.	5 grs. twice, an hour apart.	Very shortly after second dose.	Great weakness; cold extremities; fluttering pulse, and subnormal temperature.	Short.	Recovery.	Penney. Times and Register, June 22, 1889, p. 183.	Not stated.	Typhoid fever.	Temperature above 104°.
13	M.	10 grs. every 4 hours.	Very soon; after a few doses.	Great cyanosis; weak, compressible pulse, pinched features, and great weakness.	24 hours.	Recovery.	Vineberg. New York Med. Jour., 1887.	Not stated, but delicate.	Typhoid fever.	
		10 grs., followed by 5 grs.	In 2 hours.	Cyanosis of entire body; profuse sweating, subnormal temperature, and collapse.		Recovery.	Sexton. Cinn. Lancet-Clinic, 1887.		Acute miliary tuberculosis.	
		0.25 gr.		Collapse.		Recovery.	Pavai-Vajna. Therap. Gazette, 1887.			
				Sweating and adynamia; cyanosis and hæmorrhage.		Recovery.	Dulacska. Deutsche Med. Zeit., 1887.			
				Sweating, cyanosis, and hæmorrhage.		Recovery.	Dulacska. Deut. Med. Zeitschrift, 1887.			

UNTOWARD EFFECTS OF ANTIFEBRIN, No. 3.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
				Clonic convulsions; cyanosis.		Recovery.	Biro. Deut. Med. Zeitschrift, 1887.			
7	M.	7½ grs. hourly till 30 grs. were taken.	At once.	Temperature, 95° F.; almost pulseless; collapse.	6 or 7 hours.	Recovery.	New Orleans Med. and Surg. Journal, 1887.			Given by mistake.
		8 grs. every 2 hours.		Profound collapse and cyanosis.		Recovery.	Trost. Kan. City Med. Index, 1887.		Intermittent fever.	
						Recovery.	Cesari and Buroni. Deut. Med. Zeitschrift, 1887.			
Child.		4 grs. every 2 hours for a day.	In a few hours.	Died in cyanosis and collapse.	A few hours.	Death.	Von Quast. Deut. Med. Zeitschrift, 1887.			Against physician's orders.
13	F.	2 doses of 4 grs. each.	After second dose.	Cyanosis; great faintness, palpitation, and prostration.	24 hours.	Recovery.	Meyer. London Lancet, June 8, 1889.	Resistant to action of drugs generally.	Headache.	
60	F.	8 grs. in one dose.	In 15 minutes.	Profuse sweat; some depression; signs of heart-clot.	A few hours.	Death.	Meyer. London Lancet, June 8, 1889.	Infirm.	Acute pneumonia with high fever.	Death due to heart-clot (?).
	F.	3 to 4½ grs.		Cyanosis.		Recovery.	Bauer. Therapeutic Gazette, 1887.			

UNTOWARD EFFECTS OF ANTIFEBRIN, No. 4.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
Adult.	F.	Not known.	In 3 hours.	Vomiting; cold sweat: syncope; pupils dilated; heart beating violently; curious mental state of semi-unconsciousness.	24 to 36 hours.	Recovery.	Goll. Deut. Med. Zeitung, 1887.		Nervous headache.	
							Heinzelmann. Münch. Med. Woch., 1887, No. 3.			
38	M.	30 grs. twice in 24 hours.	¼ hour after last dose.	Great depression; cold sweats; vertigo; anxiety; rapid pulse; blue hands and face.	Several days.	Recovery.	Apothetic. Zeitung, 1888; also, Med. News, January 12, 1889.	Not stated.	Headache.	
Adult.	F.	5 grs. every 4 hours; 3 doses.	After several doses.	Cyanosis; lips and finger-nails a dark blue; pulse feeble.	A few hours.	Recovery.	Winner. Therap. Gaz., 1887, p. 646.	Not stated.	Tonsillitis.	
Adult.	F.	60 grs. at one dose.	After the first dose.	Blueness of lips and fingers; temperature, 97° F.; no sweat; severe headache.	A few hours.	Recovery.	Gibbons. Maryland Med. Jour., July 6, 1889, p. 183.	Not stated.	Headache.	
28	F.	4½ grs. in one dose.	After the single dose.	Severe collapse; fall of temperature.	A few hours.	Recovery.	Sembritzki. Therap. Monatshefte, June, 1889, p. 267.	6 months advanced in pregnancy.	Typhus fever.	Child born at term in good health.
27	F.	1½ grs. in one dose.	After a single dose, at once.	Profuse sweat and collapse.	A few hours.	Recovery.	Sembritzki. Therap. Monatshefte, June, 1889, p. 267.	Not stated.	Gastric fever.	

UNTOWARD EFFECTS OF ANTIFEBRIN, No. 5.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
19	F.	5 grs. in one dose.	At once.	Marked collapse; pulseless; cold; no lividity.	A few hours.	Recovery.	Occurred in my own wards.	Phlegmatic	Typhoid fever.	
Adult.	F.	60 grs. in one dose.	Almost at once.	Deathly pale; unconsciousness; screaming, as if in pain; pulse rapid; skin cold; finally cyanosis.	2 days.	Recovery.	Furth. Wiener Med. Presse, April 21, 1889.	Not stated.	Headache.	
Adult.	M.	2½ grs. at 9, 2, 10, 3, and 11 o'clock.	After last dose.	Chill; great cyanosis; clonic twitchings of extremities; rapid breathing; pulse very slow; collapse.	24 hours.	Recovery.	Alisch. Therap. Monatshefte, July, 1889.	Not stated.	Acute gastritis.	
34	M.	15½ grs. every hour for 5 doses.	In about 2 hours.	Violent diarrhœa; cyanosis; weakness; dizziness; slight fever.	10 days before well again.	Recovery.	Münch. Med. Woch., No. 19, 1889.	Not stated.	Fever.	
Adult.	M.	170 grs. of drug in one dose.	In 30 minutes.	Intoxication and somnolence; intensely cyanotic; great weakness; pain near heart; profuse sweat.	1 day.	Recovery.	Allison. Jour. Amer. Medical Assoc'n, Jan. 19, 1889.	Not stated.	Not stated.	
29	M.	92 grs. in 2 equal doses, in 4 hours.	At once.	Alarming cyanosis; a rapid pulse; no changes could be found in blood.	3 days.	Recovery.	Freund. Deutsche Med. Woch., xiv, p. 41, 1888.	Not stated.	Not stated.	

UNTOWARD EFFECTS OF ANTIFEBRIN, No. 6.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
34	M.	Five 1-grain powders at intervals of 1 hour.	In a few minutes after last dose.	Skin, conjunctiva, lips, and mouth were blue; urine gave reaction for aniline; temperature subnormal; diarrhœa.	10 days.	Recovery.	Panschinger. München. Medicinische Woch., 1889, No. 19.	Healthy.	Thought he had fever.	
19	M.	10 grs. in one dose.	In 15 minutes.	First skin was reddened, and a profuse sweat came on; coldness; semi-conscious; in four hours was moribund.	1 day.	Recovery.	Wilding. British Med. Jour., September 14, 1889.	Not stated.	Acute pulmonary tuberculosis.	Died of disease after 14th day.

The result of an analysis of these reports is very reassuring to those who have patients so affected, for in only 3 cases did death occur. In 1 of these the dose was a single one, exceedingly large in amount; in another, the drug was used in large doses during twenty-four hours; while in the third the real cause of death was thought to be heart-clot. In no instance, therefore, did death occur from an ordinary dose in an uncomplicated case.

In regard to the diseases in which untoward effects are most commonly seen, we find that the following list answers this question very well:—

"Fever,"	1 case.
Typhoid fever,	7 cases.
Miliary tuberculosis,	1 case.
Intermittent fever,	1 case.
Headache,	5 cases.
Tonsillitis,	1 case.
Gastric fever,	1 case.
Acute gastritis,	1 case.
Phthisis,	2 cases.
Not stated,	1 case.
Pneumonia,	2 cases.
Typhus fever,	1 case.

As in the tables of the untoward effects of antipyrin, so here do we find that the reporters so frequently failed to mention the temperament of the patient and his occupation that too little material can be obtained from which to make any calculations as to these points.

Use in Fever.—The employment of the drug antifebrin in fevers must depend very much upon the exact condition of the patient and the form of his disease. As has already been pointed out, the mere presence of a malady, or of a high temperature, cannot, correctly speaking, be an indication for any particular remedy.

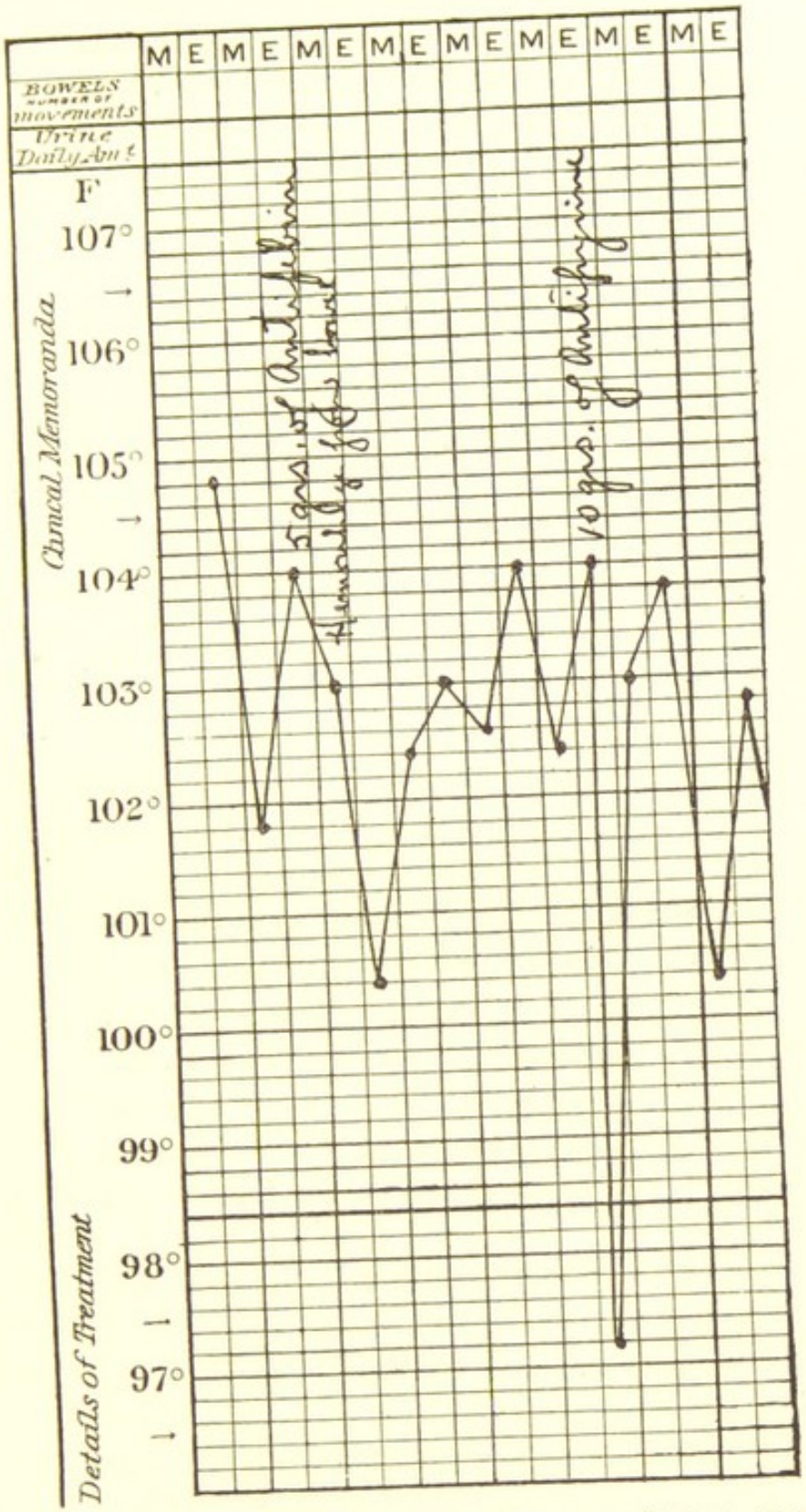
The phase of the disease must be recognized and the question as to whether the fever which is present is harmful must be duly weighed. If such attention is not paid we at once have to do with the bane of medicine,—meddlesome therapeutics.

Though a number of writers have claimed that certain antipyretic remedies of equal power act with different results in different diseases, the writer has never seen any such differences, and we must be guided rather by our individual experience as to the value of some particular antipyretic in all diseases than by any other rule. The question is rather what is the best antipyretic for all cases than what is the best one to use in this or that case, provided, of course, that no idiosyncrasy exists to any one of them.

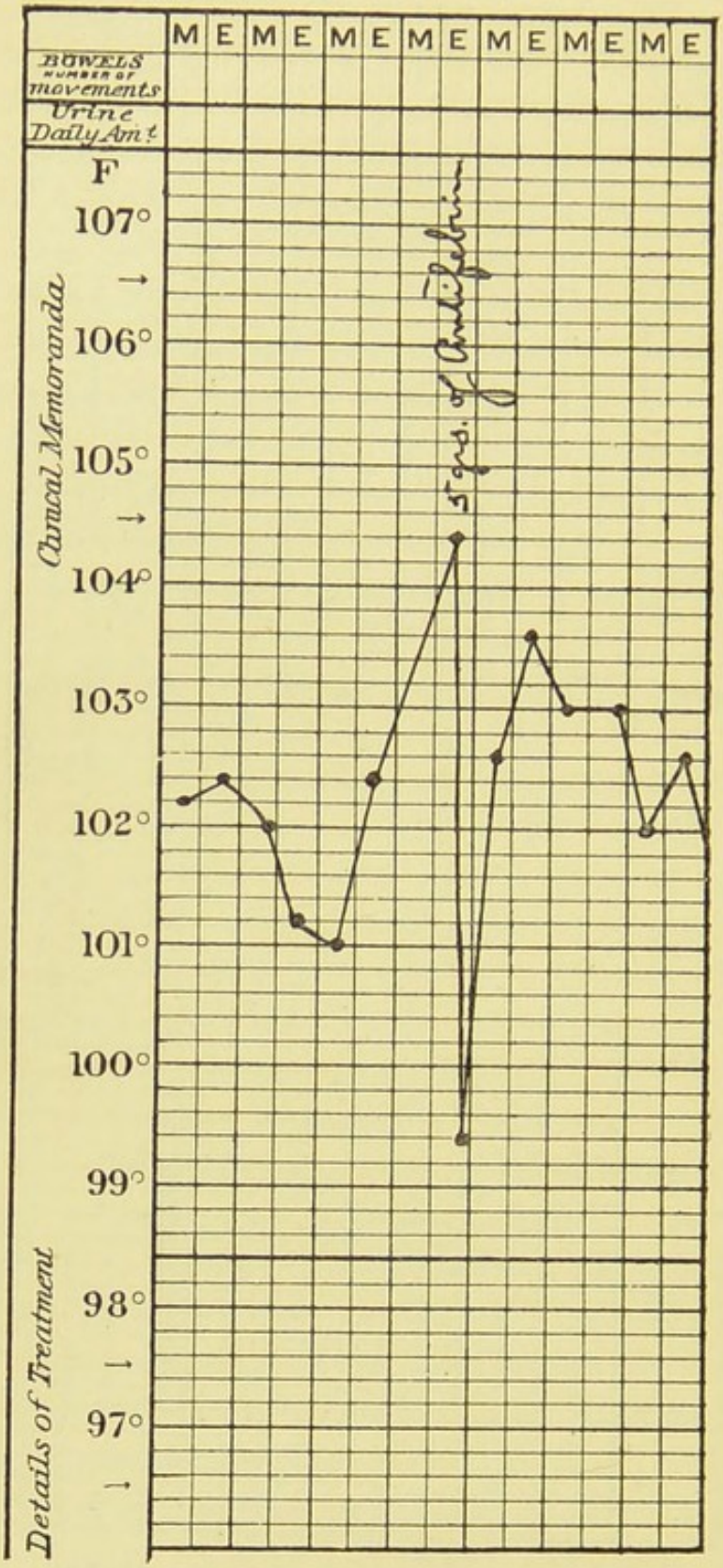
All observers are not in accord, however, as to which is the best antipyretic. While the writer has heard phenacetin spoken of most highly by some authorities, he has heard it equally severely condemned by others; and though Ringer prefers antipyrin, Mitchell Bruce relies chiefly upon antifebrin. In America almost every one prefers the former drug, and the general diffusion of this preference apparently rests not so much upon published facts as upon personal experience. While the number of cases of ill effects recorded is small with antifebrin as compared with those of antipyrin, the idea prevails, and perhaps justly, too, that the former is much more capable of harmful deeds than the latter, and it cannot be denied that scientific basis of great weight exists for this belief.

According to Eisenhart,[1] the antipyretic influence of antifebrin is not manifested for fully two hours after its administration, when it appears with a profuse

[1] Münchener Med. Wochenschrift, No. 47, 1886.



TEMPERATURE CHART OF CASE OF TYPHOID FEVER, SHOWING THAT ANTIFEBRIN IS NOT SO POWERFUL AN ANTIPYRETIC AS ANTIPYRIN.



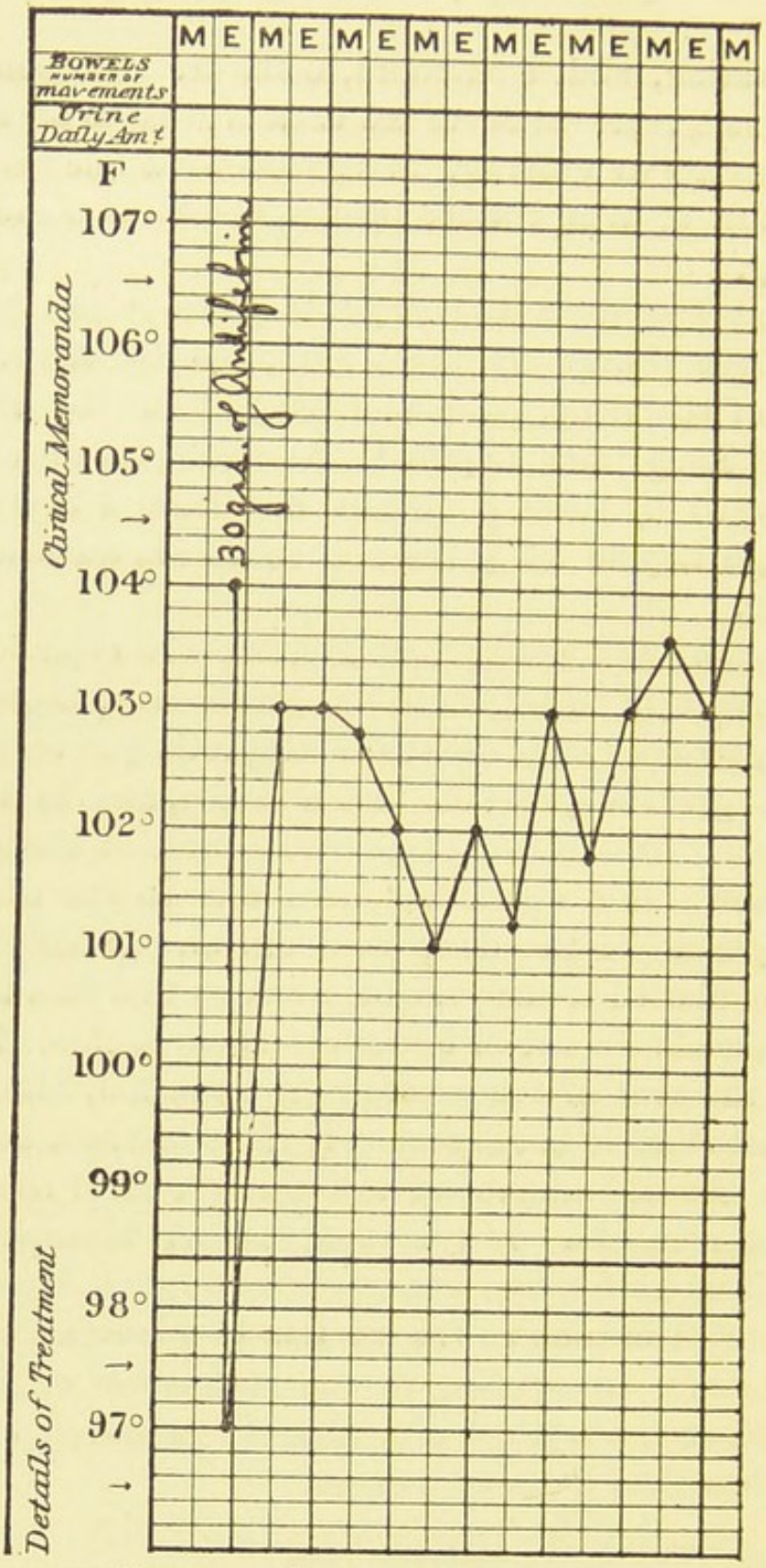
TEMPERATURE CHART OF CASE OF TYPHOID FEVER IN WHICH ANTIFEBRIN PRODUCED A GOOD EFFECT.

perspiration, and, sometimes, collapse. He concludes that small, repeated doses are useless; that to obtain any good results we must use all we wish to at one time, and, if no fall of temperature occurs, resort to some other remedy.

That Eisenhart is correct in these views has not only been proved by the writer, but by the original users of the drug, Cahn and Hepp,[1] and by Heinzelmann,[2] Lang,[3] and Lepine.[4] As a rule, the dose of the drug used by these clinicians was from 4 to 8 grains, although Lepine has given the enormous quantity of 1 drachm.

Typhoid and Other Low Fevers.—In typhoid fever the studies of most clinicians show that, though the drug possesses very decided antipyretic power, it often causes great depression and collapse, and in no way influences the duration or general course of the disease. How much this result has been due to the excessive employment of the drug is doubtful, but that it has been so abused seems evident, when we find that Lepine[5] recommends the use of 8 grains an hour, before the time when the rise of temperature is expected, though he confesses that in those seriously ill he has seen cyanosis, with a lessened amount of urine, assert itself as a result of such methods. In the same manner, Mousset,[6] who worked under Lepine, recommends two such doses daily, and a third as soon as the system becomes accustomed to the drug. According to the statements of Mousset himself, such a method of treatment produced cyanosis in no less than 3 out of 7 cases.

[1] Centralblatt für klin. Med., Sept., 1886.
[2] Münchener Med. Wochenschrift, No. 3, 1887.
[3] Wien. Med. Presse, May 29, 1887.
[4] La Semaine Méd., p. 473, 1886.
[5] *Ibid.*
[6] Lyon Médicale, 1886, liii, p. 309.



TEMPERATURE CHART OF CASE OF TYPHOID FEVER IN WHICH AN EXCESSIVE DOSE WAS ADMINISTERED THROUGH AN ERROR ON THE PART OF A NURSE.

The sweating, sometimes produced in excessive amounts, may prove a just cause for the non-employment of the drug in typhoid fever. Numerous cases have come under the author's notice where this state existed, and Osler has noted that the profusion of the sweat may be so great as to utterly prohibit its use.

By far the most exhaustive study of the effects of antifebrin in typhoid fever that we have seen is that of Guttmann,[1] who treated no less than 81 cases with the drug, giving 7 grains night and morning, except at about the twelfth or fourteenth day, when one dose was sufficient. He thinks that small, repeated doses are useless and without any effect, yet so confident is he of the power of the drug in doing good, if used properly, that he thinks it quite as efficacious as the cold bath, and better, in typhoid fever, than any other remedy of its class.

The reason for Guttmann's preference for antifebrin to antipyrin is found in the diminutive dose of the former as compared to that of the latter, for he states that he discovered that it required as much as 60 or 70 grains of antipyrin twice a day to produce the effects seen after the use of 7 grains of antifebrin, night and morning. He also noted that the apyrexia of antipyrin only lasted about four hours, while that of antifebrin was of much longer duration.

On the other hand, it is claimed by Secretan[2] that the reverse is the case, and that antipyrin is far superior to antifebrin in the permanence of its action. Demme[3] also makes a similar assertion, and the writer, from his own observations, is inclined to agree with him. Very

[1] Berliner klin. Wochenschrift, 1887, p. 942.
[2] Revue Médicale de la Suisse Romande. 1886.
[3] Internationale Klin. Rundschau, No. 4, 1888.

frequently in the St. Agnes Hospital this fact has been noted, and Guttmann is certainly incorrect in his assertions. At the same time, the writer must confess that his experience is fully in accord with that of Guttmann in respect to the effect of large doses given at long intervals; in every instance where the two methods have been tried by the writer the small doses, frequently repeated, have failed, where the others produced an effect not only of a much more marked character, but more prolonged. That Guttmann has the support of some clinicians is undeniable, but that certain investigators have obtained good results from small, frequently repeated doses cannot be gainsaid. Thus, Way[1] has so used antifebrin in 13 cases of typhoid fever and reached good results. He thinks that the effective dose is so small as compared to the poisonous dose as to make the drug perfectly safe. A study similar to that of Guttmann, made by Faust, reached results of a satisfactory character, the drug being used in 29 cases of enteric fever. Faust noted, when the temperature rose rapidly and was accompanied by a chill, that he was able to prevent this exacerbation by a dose of the drug, just as the rigor was beginning. Curiously enough, he is also responsible for a recommendation which flavors of *similia similibus curantur*, which we cannot understand, namely, that the use of a small amount of antifebrin immediately after the use of the cold bath in typhoid fever prevents any subsequent chilliness and quiets the patient. If this is true the drug must exert a balancing power over the heat-centres.

We have already spoken of the fact that all writers are in accord in stating that antifebrin does not influence the

[1] Medical News, 1887, vol. i, p. 241.

duration or course of typhoid fever except by an indirect action. It is, however, very important for us to discover whether the condition of the patient is for the time being really improved. The writer is sure that the answer should be in the affirmative, and there is an overwhelming amount of testimony in favor of such a belief. Thus, Faust found that all his cases felt better, seemed more intelligent, and had a cleaner-looking tongue, with less anorexia, when the drug was used. Cahn and Hepp have also stated that the peculiar drowsy, stupid face of such cases brightens up if the drug is given, and there can be no doubt but that this is true.

While antifebrin has been greatly praised by writers in Europe, in America it has not been thought of so highly. Cohen,[1] in an article upon its employment in typhoid fever, has done anything but praise it, as he found it far more dangerous than antipyrin. He also noted that it was less enduring in its effects,—a conclusion which agrees with the statement of Demme and Secretan, already given. Greene[2] has recorded instances in which the drug absolutely failed where antipyrin succeeded, and the writer has frequently turned from antifebrin as useless, in safe doses, to receive aid from the antipyrin.

The value of antifebrin in phthisis is doubtful, since, although it greatly affects the temperature, it is very apt to cause collapse, profuse sweating, and depression. Thus, the writer has seen cases of phthisis where the attempt to control the fever by antifebrin resulted in the manner named, and Riese[3] points out, what the

[1] Medical News, Oct. 8, 1887.
[2] University Med. Magazine, Jan., 1889.
[3] Deutsche Med. Wochenschrift, 1886, 835.

writer has also noted, namely, that in this disease cyanosis is very apt to come on. Weill[1] also believes it is contra-indicated in tubercular hectic fever, and in this he is indorsed by Pavai-Vajna.[2] On the other hand, Cauldwell,[3] after trying it in 30 cases, came to the conclusion that it is the best drug with which to combat the fever and accompanying evils of phthisis. In the face of such contradictory testimony some confusion arises, but the author is confident that he is correct in believing it harmful rather than of good effect.

Sthenic Fevers.—It at once becomes evident to the most careless student of medicine that a drug absolutely unsuited to a case of asthenic disease may, on the other hand, agree with a scarlet-fever patient very well, or that the reverse may be true.

In consequence of this we find that the sweating of antifebrin is not marked or troublesome in acute sthenic diseases, and that in consequence it more rarely causes collapse. In measles and scarlatina both Ginsburg and Widowicz[4] speak highly of its use, and the former thinks it is better under such circumstances than is antipyrin. That these assertions are based upon fact seems positively proved, and that there is a reason for them is also apparent.

Most of the exanthematous diseases are those of childhood, and there is a vast amount of clinical evidence showing that these drugs are particularly efficacious and devoid of untoward influence in young persons. Lowenthal,[5] Demme,[6] Love,[7] and Guttmann,

[1] Tribune Médicale, 1887, xix, 195.
[2] Centralblatt für die Gesammte Therapie, 1886.
[3] N. Y. Medical Record, 1887, xxxi, p. 426.
[4] Wien. Med. Wochenschrift, 1887, p. 529.
[5] Therapeutische Monatshefte, Sept., 1887.
[6] Internationale Klin. Rundschau, No. 4, 1887.
[7] Journal American Medical Association, 1887.

as well as myself, have found this to be the case. In small-pox Haas has found that in confluent cases antifebrin lowers the temperature and relieves the nervous irritation, altogether exercising a desirable influence.

Rheumatism.—The employment of antifebrin in rheumatism may be separated, if desired, into that devoted to the cure of the disease with the relief of pain and the reduction of pyrexia. There can be no doubt whatever of the ability of the drug to control the fever of this disease, but the question as to whether it favorably influences the progress of the malady is to be decided.

We have already spoken of the studies of Guttmann upon the antipyretic power of antifebrin, but it should not be forgotten that he has also used it far more in rheumatism,[1] as he has employed it in 52 cases of acute, 29 cases of chronic articular rheumatism, and in 167 cases of "general rheumatism," making in all no less than 248 cases. The conclusions which are to be drawn from this immense mass of material seem to be that as a specific against the disease the remedy is equal to salicylic acid, antipyrin, and salol, and in some directions seems even better than they are. The dose used by Guttmann was from 7 to 15 grains once or twice daily, and he records the fact, which is scarcely credible, that in none of these cases did cardiac involvement ensue. Guttmann is supported in these statements by the experience of Cahn and Hepp,[2] Landgraf,[3] Riese,[4] Moore,[5] Munn,[6] Destree and Slosse,[7] Charpentier,[8] Faust,[9] and

[1] Berliner klin. Wochenschrift, Dec. 12, 1887.
[2] *Ibid.*, 1887, xxiv, p. 26.
[3] Deutsche Med. Wochenschrift, 1886, No. 47, p. 839.
[4] *Ibid.*, 1886, xii, 835.
[5] Weekly Medical Review, April 28, 1887.
[6] Physician and Surgeon, Sept., 1887.
[7] Journal de Méd. de Chirurg. et de Pharm., June 20, 1887. [8] *Ibid.*
[9] Deutsche Med. Wochenschrift, 1887.

Pavai-Vajna,[1] who believes it equal to salicylic acid. Weinstein[2] believes antifebrin to be a specific in rheumatism.

Somewhat opposed to these testimonials are the conclusions of Eisenhart,[3] Fadella,[4] and Poutta, as well as those of Lepine,[5] Snyers,[6] and Sarda,[7] who believe that antifebrin, while possessing antirheumatic virtues, is, nevertheless, far inferior to the salicylates. From the author's own studies of a large number of cases of rheumatism, he is forced to take a position half-way between the opinions just given. He has seen cases of acute articular rheumatism improve remarkably under antifebrin, and he has also seen it fail as utterly. The two following cases are illustrative of this:—

Case 1.—M. T., aged 45, male. Was admitted to the writer's wards in the St. Agnes Hospital for a severe attack of acute articular rheumatism. The left elbow was greatly swollen and inflamed, and a bursitis had been set up. Both feet and ankles were greatly enlarged. The lumbar muscles were also affected and the left hand was badly swollen. Antifebrin, in the dose of 5 grains three times a day, rapidly relieved him, so that he was able to be out of bed on the fourth day.

Case 2.—S. A., aged 19, domestic. Was admitted to the same wards in the St. Agnes Hospital for acute articular rheumatism, involving the left arm and both knees. There was a systolic murmur at the mitral valve. Antifebrin in 5-grain doses three times a day had no effect.

[1] Centralblatt f. die Gesammte Therapie, Aug., 1887.
[2] Wiener Med. Blatt., 1887, 159, 200.
[3] Münchener Med. Wochenschrift, Nov. 23, 1886.
[4] Osservator Turin, 1887, p. 409.
[5] Lyon Médicale, 1886-87, iii, p. 269.
[6] Annales Soc. Méd. Chir. de Liege, 1886, xxv, p. 499.
[7] Bull. Gén. de Thérapeutique, May 30, 1888.

It is but just to say that nothing else did her any good as far as we could tell. Sixty grains of salicylate of sodium a day were ineffectual.

These 2 cases show just what the author's experience has been in many instances. We must regard antifebrin as one of the drugs to be tried in all cases.

Nervous Affections.—In much the same manner as antipyrin was found, some time after its introduction, to be possessed of pain-relieving power, so antifebrin has also been discovered to possess similar properties,—a discovery the credit of which must be given to the French investigator, Lepine,[1] who has written upon this subject, at various times, very exhaustively. Almost every form of nerve-pain seems to indicate its employment, and it has been successfully used in the crises of ataxia, the agonizing dartings of gastralgia, and even in chorea, with good results. In a corresponding manner Secretan[2] has obtained brilliant effects in cases of sciatica, and Silva[3] has seen the most obstinate headache yield to its influences.

One of the best papers on antifebrin as a nervine is that of Demieville,[4] who studied a series of cases with considerable care. He has shown that within half an hour after its administration the relief from the pain begins to appear, and that by one hour or two hours total relief is attained. Signe, under Grasset's direction, has reached similar results, and Dujardin-Beaumetz[5] is loud in the praises of the analgesic effects obtained by him. In a similar manner Fischer,[6] of

[1] Revue de Médecine, 1886.
[2] Revue Méd. de la Suisse Romande, 1887, vii, 29.
[3] Western Medical Reporter, 1886.
[4] Revue Méd. de la Suisse Romande, June 15, 1887, p. 305.
[5] Therapeutic Gazette, vol. x, 1887.
[6] Münchener Medicin. Wochenschrift, No. 23, 1887.

Canstatt, in 10 cases of tabes dorsalis, corroborates the views just expressed, for among the 10 cases to whom the drug was given ninety times it failed only once. In hemicrania and in "brow ague" it also seems to be of service, and it would be hard to find a more widespread indorsement of any drug for the relief of pain than is made of this one.

Thus, Humston,[1] Clark,[2] Hirsch,[3] Talcott,[4] Ademski,[5] Munn,[6] Warfringe,[7] Stewart,[8] Merkel,[9] Morton,[10] Proudfoot,[11] McConnell,[12] Huthins,[13] and a number of others have published statements to this effect.

Antifebrin has also been found of value in epilepsy by the writer, Borosnyoi,[14] Fischer,[15] Salm,[16] and several others.

[1] Medical and Surgical Reporter, January 14, 1887.
[2] Chicago Medical Times, September, 1887.
[3] Therapeutische Monatshefte, October, 1887.
[4] Chicago Medical Times, October, 1887.
[5] Vratch, No. 27, 1887.
[6] Physician and Surgeon, September, 1887.
[7] Hygeia, Stockholm, August, 1887.
[8] Canada Medical Record, January, 1887.
[9] Münchener Med. Wochenschrift, June 12, 1887.
[10] American Practitioner and News, January 21, 1887.
[11] Canada Medical Record, January, 1887.
[12] *Ibid.*
[13] Weekly Medical Review, May 19, 1887.
[14] British Med. Journal, April 28, 1887.
[15] *Loc. cit.*
[16] Neurologische Centralblatt, 1886.

THALLIN.

Experimental Evidence.

Although thallin is a very much older drug than antifebrin, being a contemporary of antipyrin, yet our knowledge of its physiological action is as yet very limited, as are also, indeed, our clinical observations. For some unknown reason this drug has been placed in the background largely without sufficient cause, since very few legitimate claims are made against it, and a large number of reliable clinicians have spoken of it in high praise.

Heat Functions.—In a very extended series of experiments carried out by Tschistowitsch[1] with thallin upon rabbits and dogs, he found that when the drug was given to normal afebrile animals in the dose of from $\frac{1}{4}$ to $\frac{1}{2}$ grain for each $2\frac{1}{2}$ pounds of the animal's weight, or, in other words, when a dose was used which approached in its proportions those commonly employed in clinical medicine, no marked or constant change ensued in the bodily temperature, although the tendency was naturally toward depression rather than exacerbation. It is also asserted by this observer that he could find no direct relationship existing between the quantity of the drug employed and the fall of temperature produced. As the research of Tschistowitsch seems to have been most carefully carried out, the writer has not thought it necessary to repeat his experiments, particularly as he used the drug by the stomach, the rectum, intra-venously, and subcutaneously. As he

[1] Ieshenedjelnaja Klinitscheskaja Gazeta, No. 30, 1885.

employed two varieties of animals, there can be no doubt of the correctness of his results, and they have been confirmed by Jaksch, Pisenti, and Maragliano.

Passing on from the question as to the influence of thallin upon normal bodily heat, we find that in the fevered animal as well as in man the drug acts with very considerable power, and in direct proportion to its dosage. Not only have we the experiments of Tschistowitsch on this point, but, in addition, we learn from those of Martin[1] that such a fall takes place even though the febrile action is dependent upon an injury to the inhibitory heat-centre of Ott in the corpus striatum. The very large amount of clinical evidence confirmatory of these statements renders them incontrovertible, and it only remains for us to know how this fall in bodily heat is brought about. From the experiments of Martin, in the research already referred to, we find that the fall of temperature in the fevered dog is produced by an increase in heat dissipation in every instance, although it is to be noted that in two of the six experiments made by him the drug failed entirely to control the fever. It was also found by Martin that thallin influenced heat production very irregularly. In three instances it was increased and in three diminished. It would therefore appear that the chief action of the remedy is its influence on the elimination and not on the manufacture of heat units.

In a series of studies, which seem to be of little value, Anserow, in the *Russian Medical Review* for April, 1886, found that, *pari passu* with the internal fall of temperature in the dog, under thallin, a rise of temperature in the paw and peripheral portion of the body occurred; and, without any good reason, he comes to the conclu-

[1] Therapeutic Gazette, May, 1887.

sion that this phenomenon is due to an exhaustion of the heat functions of the body,—a conclusion at once as remarkable as it is unfounded and unnecessary, since the mere dissipation of heat from the periphery of the body may temporarily cause such a condition.

Circulation.—The influence of thallin upon the circulation in the lower animals, when in a healthy state, varies, very naturally, with the dose exhibited. As may be seen from the tracings which follow (pages 108*a* to 108*f*), the drug causes a fall of arterial pressure, with an accompanying slowing of the pulse, when injected intravenously in full dose. As these results are but a counterpart of those of Tschistowitsch, they may be accepted as well founded and correct.

That the influence on the circulation in moderate amounts is, however, very slight, is shown not only by the tracings herewith appended, but by the assertions of the Russian investigator, who has found very slight alterations in blood-pressure in fevered animals.

The fall of blood-pressure when large doses are employed is due to direct depression of the peripheral vasomotor system, and, to a slight extent, to a depression of the heart itself.

Antiseptic Action.—Tschistowitsch has noted that a solution of one-tenth of 1 per cent. of thallin prevents the alcoholic fermentation of grape-sugar, and that a solution of 5 per cent. absolutely inhibits such changes. These results have been indorsed by those of Kries, who has found that a 4-per-cent. solution is capable of destroying microbes, and Goll has put the subject to a practical test by using the drug in a 2-per-cent. solution for the treatment of gonorrhœa. Similarly, Pisenti, in Albertoni's laboratory, has found thallin to possess properties which prevent the putrefaction of urine.

Toxic Effects from Prolonged Use.—Very few reports of such a condition as this heading indicates are on record, and one of the most interesting of these is that of Ehrlich,[1] in which a case was given thallin in small, but frequently repeated, doses for forty-two days. At the post-mortem examination the kidneys were found greatly enlarged and covered by numerous white spots. The ends of the papilla were also covered by a hæmorrhagic, discolored deposit. That such changes are produced by thallin seems proved by the fact that Ehrlich has seen exactly similar changes in dogs under the same conditions.

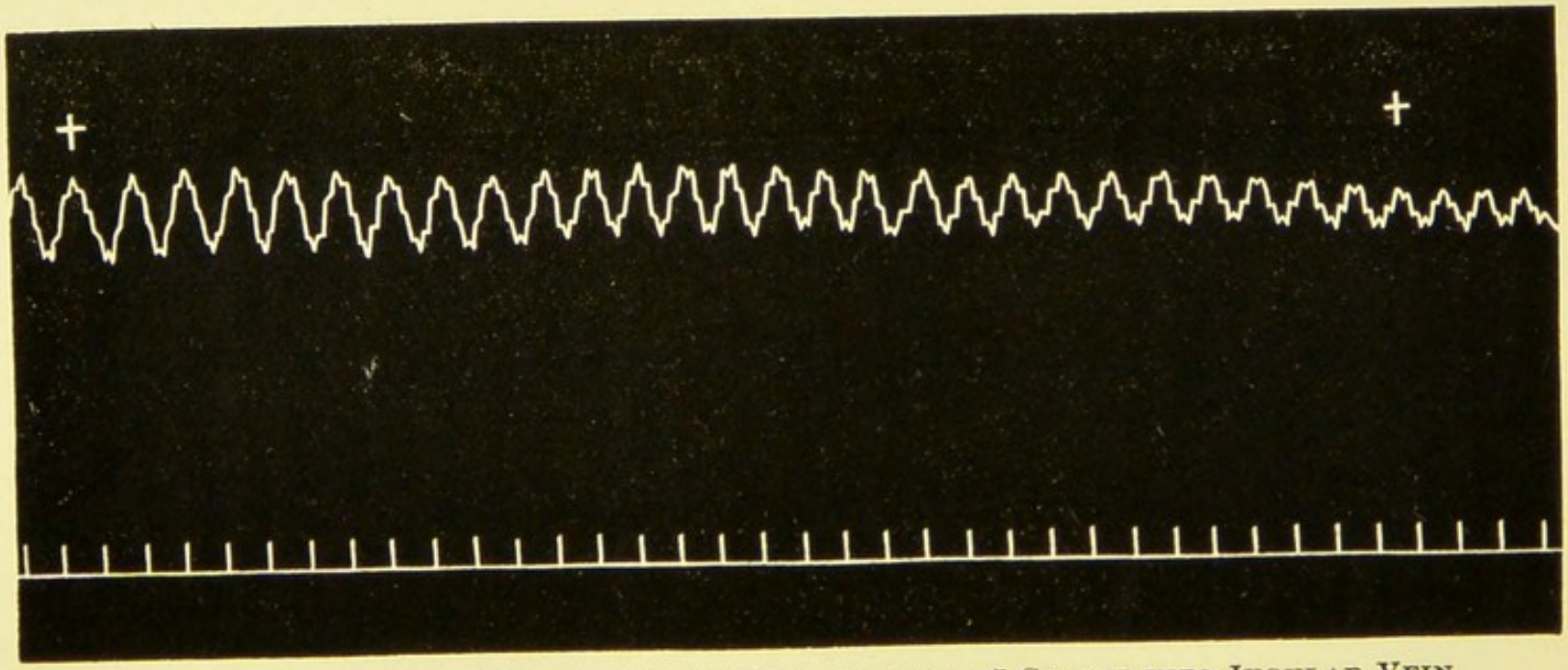
By far the most complete studies upon this question, however, are those of Pisemski,[2] who, giving the drug hypodermically, found that in rabbits, in the daily dose of 3 grains, death ensued on the sixteenth to twenty-eighth day, or, if the dose was 6 grains, the animal died in one day. In the dog it was found that the daily dose of 5 grains produced death in twenty-five to twenty-eight days.

The changes found post-mortem by Pisemski were as follow: In the brain, lungs, spleen, liver, and kidneys there were detected, side by side with intense congestion, quite distinct inflammatory and degenerative changes in the early stages, while at the same time a general decrease in bodily weight was most noticeable. Before death it was found that the constant use of the drug caused a primary increase, followed by a decrease, in the number of the red blood-corpuscles, which decrease ultimately was very great.

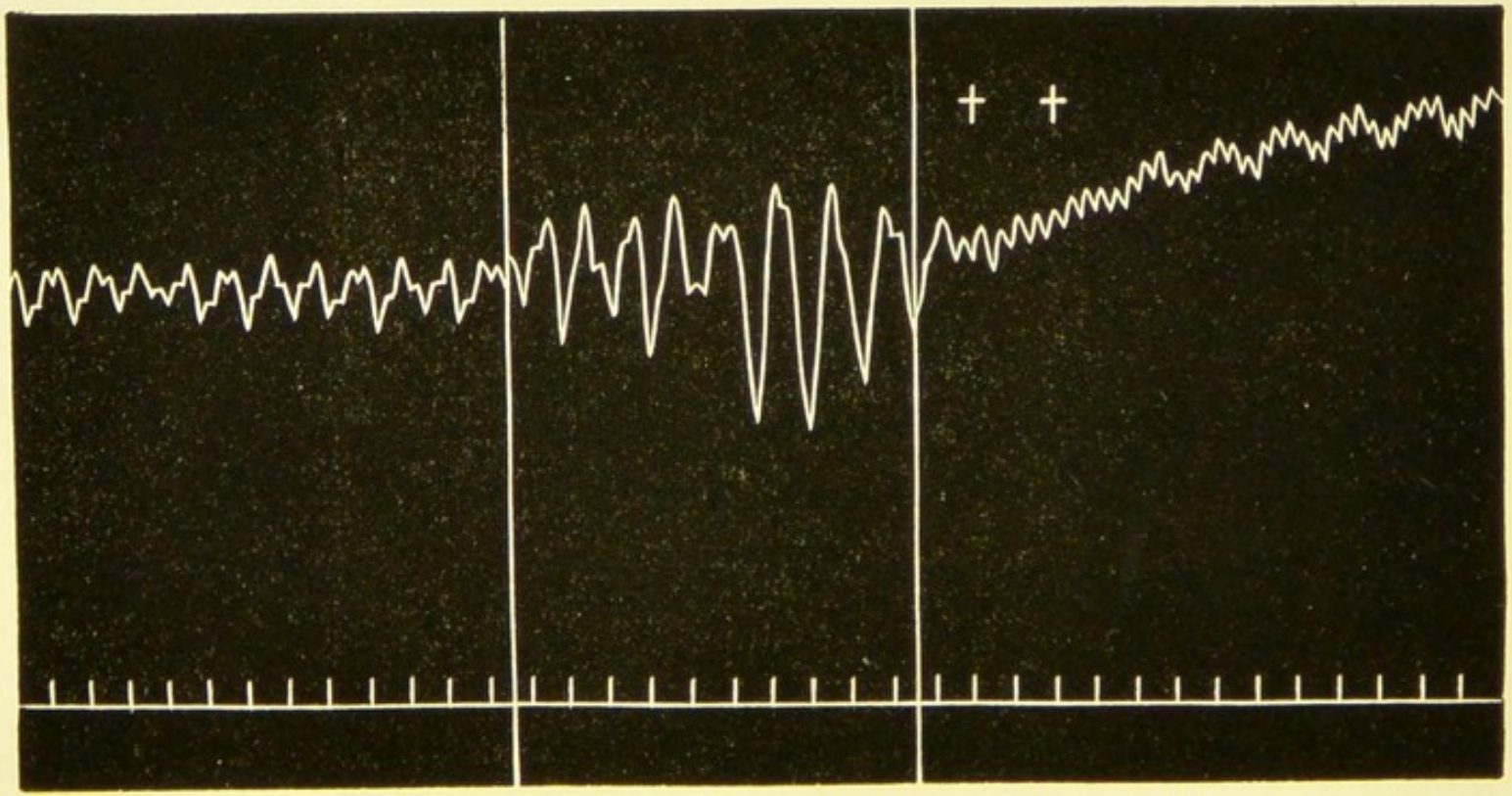
Pisemski also concludes that thallin exercises a much more irritant action on animal tissues than antipyrin.

[1] Centralblatt für die Med. Wissenschaften, Oct. 1, 1887.

[2] St. Petersburg Inaugural Dissertation, 1887, p. 48.



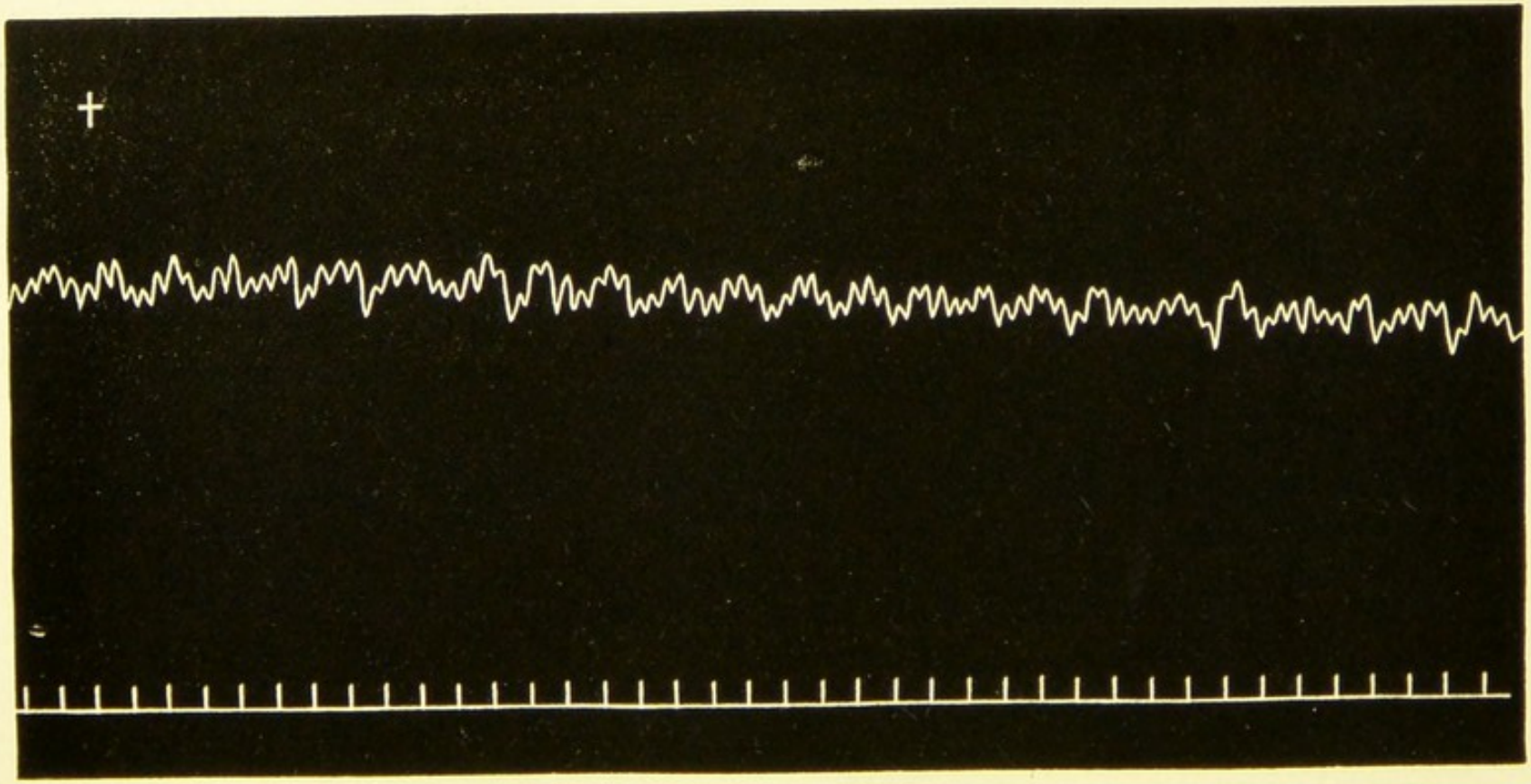
TRACING NO. 1.—DOG: WEIGHT, 16½ POUNDS. INJECTED 7 GRAINS INTO JUGULAR VEIN BETWEEN + MARKS IN 20 C.CM. OF WATER.



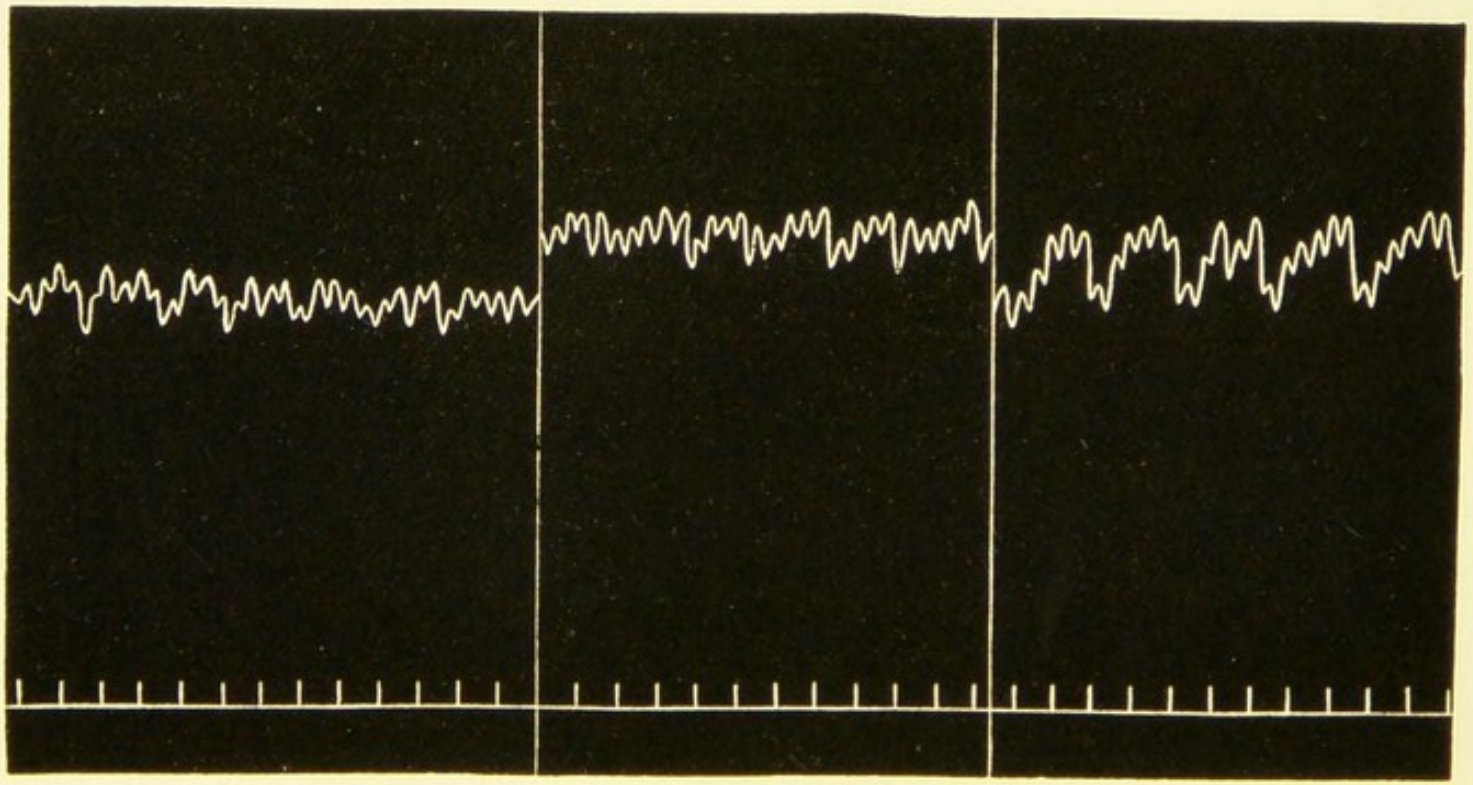
SAME CONTINUED, TWO MINUTES LATER.

SAME CONTINUED, THREE MINUTES LATER.

SAME CONTINUED; VAGI CUT AT + MARKS.



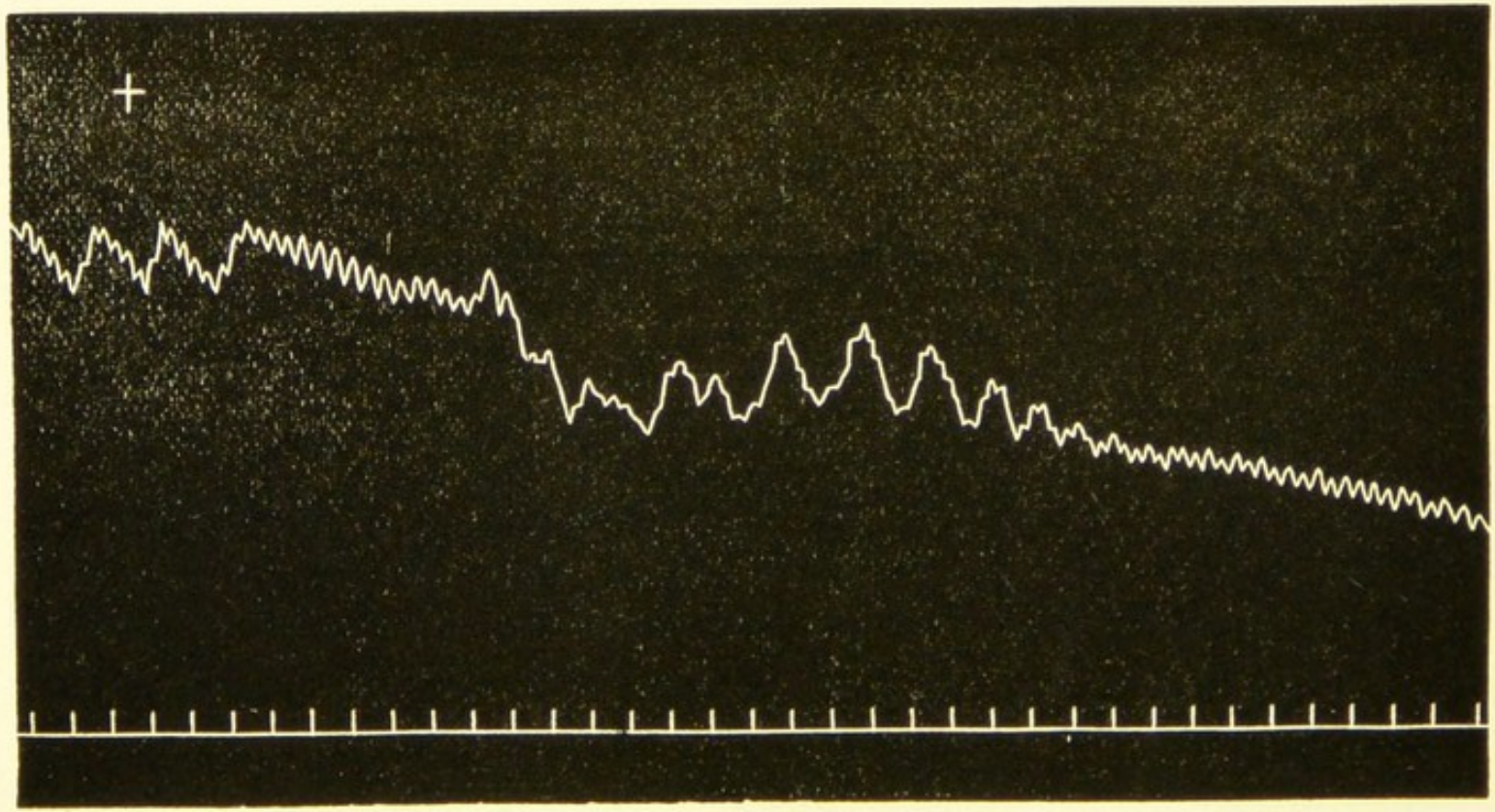
TRACING NO. 2.—DOG; WEIGHT, 17½ POUNDS. INJECTED 3½ GRAINS OF THALLIN IN 20 C.CM. OF WATER INTO JUGULAR VEIN BETWEEN + MARKS.



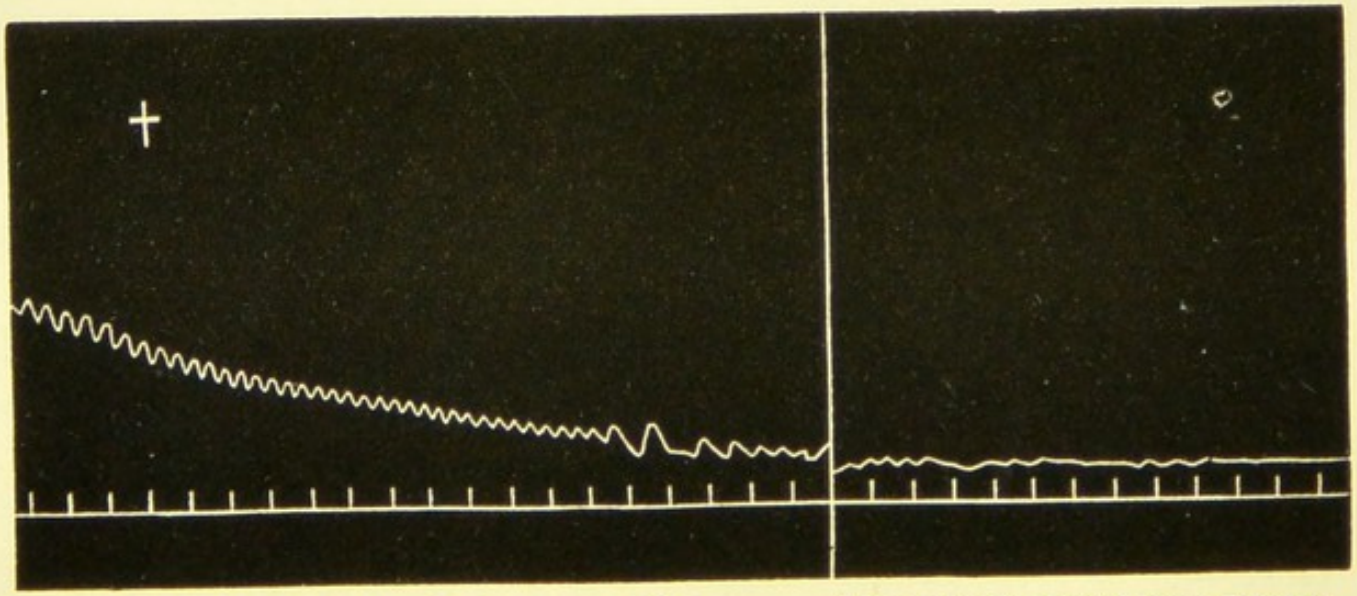
SAME CONTINUED, TWO MINUTES LATER.

SAME CONTINUED TWO MINUTES.

SAME CONTINUED, FIVE MINUTES LATER.



TRACING NO. 3.—DOG; WEIGHT, 15 POUNDS. VERY LARGE DOSE. INJECTED 15 GRAINS OF THALLIN INTO JUGULAR VEIN BETWEEN + MARK SHOWN AND THAT SHOWN ON CUT ON NEXT PAGE.



SAME CONTINUED. NO BREAK IN TIME.

SAME CONTINUED; DOG DYING.
NO BREAK IN TIME.

Tissue Waste and Elimination.—Upon tissue waste thallin seems to have comparatively little effect. Kumawaga[1] has found that in the healthy dog there is an increased elimination of nitrogen (mean increase, 6.6 per cent.). On the other hand, Karst,[2] in some experiments upon afebrile and fever patients, found that the daily amounts of urine and urea were considerably lessened, the urine becoming strongly alkaline in reaction, and he therefore thinks that the drug inhibits the elimination of oxidation products. These results are partially confirmed by Britneff,[3] who found the amount of urine decreased, with a rise in specific gravity to 1033, indicating increased solids.

On the other hand, Livierato and Predazzi[4] assert that thallin does not influence the quantity of urine passed, but that a single dose of 7 grains may cause a diminution of 5 grammes of urea in twenty-four hours, and that still larger doses cause a still greater diminution.

Upon the amount of CO_2 given off by the lungs, a dose of 15 grains caused a decrease of 6 grains of CO_2 for every 2 pounds of bodily weight.

Robin[5] has studied the effects of thallin upon the urine very thoroughly, using as subjects for his research 4 old men of from 61 to 68 years. All of them were in perfect health, although 2 of them showed slight evidences of arterial sclerosis. The doses used were from 15 to 45 grains, and the estimations were made of the uric acid, potash, sulphur, and phosphorus compounds.

[1] London Medical Recorder, Oct. 20, 1888.
[2] Vratch, No. 2, 1886, p. 32.
[3] Russkaia Meditzina, No. 1, 1886, p. 6.
[4] La Medica contemporania, July, Aug., and Sept., 1885.
[5] Archives de Physiologie, No. 4, Oct., 1889.

Upon the quantity of the urine, Robin found that the general tendency was to decrease the amount excreted daily, and out of 5 experiments there was only 1 which was not so influenced by the drug. After the drug was stopped the quantity of urine returned to the normal amount or above it.

Rather curiously, the statement is made that the specific gravity of the urine is lowered by the drug, although the amount of urine is decreased while the drug is taken. After the drug is stopped the specific gravity returns to normal. The amount of nitrogen eliminated is always diminished by thallin and the uric acid is also similarly decreased. In regard to the influence of thallin upon the phosphoric acid thrown off, Robin reached contradictory results, for in 2 cases this acid was decreased and in 2 increased. The sulphates were at first diminished, then increased, and the carbolic acid of the urine diminished during the use of the drug, but increased later on.

Robin believes that the formation of nitrogenous substances from tissue break-down is increased by the drug, but that their elimination is decreased, and that, in consequence, the drug is a dangerous one.

The drug is rapidly absorbed and rapidly eliminated by the kidneys as a combined sulphate, even when given in excess.

According to von Jaksch,[1] the addition of perchloride of iron to the urine produces an emerald-green color, and this reaction may be obtained as early as one-half hour after the introduction of the drug into the mouth, while by forty-eight hours all the drug is eliminated, according to Jaksch. Maragliano, however, found

[1] Wiener Med. Wochenschrift, 1884, No. 48.

nearly all of it eliminated in ten hours and none of it present after twenty hours.

Conclusions as to the Physiological Action of Thallin.—1. Thallin causes a slight fall in normal bodily heat.

2. Thallin would seem to lower febrile temperatures by increasing heat dissipation.

3. On the circulation the drug has a slight depressant effect, but this is of little moment. The fall of pressure occurring after large doses is due to a depression of the heart and vasomotor system.

4. Thallin in the amount of a 1-per-cent. solution possesses antiseptic power.

5. Given for a long time in toxic doses, it produces death, with internal congestions and degenerative changes in the kidneys. The blood-corpuscles are decreased in amount.

6. Upon tissue waste thallin exercises an inhibitory influence, according to some observers, and an accelerating effect, according to others. The urine is generally decreased in amount.

7. The drug is rapidly eliminated.

Clinical Evidence.

There are three salts of thallin,—the sulphate, the hydrochlorate, and the tartrate. All of them are much alike in general appearance and taste, but the sulphate is the salt most commonly employed in medicine.

Given to man in a healthy state, they produce an unpleasant taste, but no other ill effect, unless the dose has been very large; the ordinary amount of from 7 to 11 grains scarcely produces any signs at all. According to Maragliano, as much as 6 grammes may be taken in six hours without producing any gastric disturbance.

Buzzing in the ears may come on from large doses, and poisonous amounts produce labored respiration, deep cyanosis, and coma.

The only study of much value that we have is that of Maragliano, made upon healthy persons. He found that in apyretic individuals the arterial pressure does not present appreciable modifications under its use, save that for the first hour after its administration there is a slight tendency to rise, and in the second hour to fall. On the heart he thinks thallin acts as a tonic, rather than as a depressant. These results have been confirmed by the writer and by Pisenti upon the dog and rabbit (see "Experimental Evidence"), and are undoubtedly correct.

Fever.—The chief students of the action of thallin upon fever in the human being are its champion, Jaksch,[1] Maragliano,[2] Griffith,[3] Minot,[4] Nothnagel,[5] Ehrlich,[6] and Laquer, as well as Guttmann, Welt, Demuth, Oppler, Stegen, and others, among whom may be mentioned Demme and Jaccoud. The studies of Minot seem, owing to their American origin and care, worthy of special mention, as in reality outlining the general opinion and thought of practitioners on this side of the Atlantic. Minot found that thallin acted most satisfactorily and with the most lasting effect when it was given at, or just before, the end of the fastigium. The effects of the drug were always most favorable, sweating and vomiting occurring but a few times, while in many instances the patient, previously restless and delirious,

[1] Wiener Med. Wochenschrift, 1884, No. 48.
[2] Gazetta degli Ospitali, July 5, 1885.
[3] Annual of the Universal Medical Sciences, 1888.
[4] Transactions Assoc. of American Physicians, 1887.
[5] Allgemeine Wiener Med. Zeitschrift, 1887.
[6] Berliner klin. Wochenschrift, Nos. 51, 52, 1885.

became tranquil and quiet. It was also found by Minot that the drug exercises no appreciable influence upon the duration of the disease in typhoid fever, and he concludes that it is sufficiently harmless to be given to very young children.

The author's experience with thallin is too limited to admit of his speaking authoritatively concerning it, and he will therefore only state that it has always seemed to him far less useful in fevers than many of the other drugs of its class. The fact that its action is so transient,—only lasting two or three hours, as a rule,—the necessity of its frequent dosage in consequence, and its liability to nauseate the patient, by reason of its taste and action on the stomach, are all against it. That it acts quite as rapidly, if not more so, than antipyrin and antifebrin, there can be no doubt. It has been found, too, that the sweat is often very excessive, although there are some observers who assert that in children, particularly, this symptom is often absent. Jaccoud thinks that so many people have an idiosyncrasy to its use that small doses should always be used at first.

Owing to the transitory effects of the drug, repeated administrations of the remedy are necessary, and, as this fact was first pointed out by Ehrlich, the term "thallinization of Ehrlich" is frequently heard of at the present time when the drug is spoken of. The doses should be given hourly, in the amount of $\frac{1}{2}$ to 1 grain, or even 2 grains, to adults whenever it is desired to thallinize a case. In every instance its action should be carefully watched.

PHENACETINE, OR ACETPHENITIDIN.

Experimental Evidence.

The discovery on the part of Hinsberg and Kast[1] that a compound known to chemists as acetphenitidin possessed antipyretic powers led them to employ the drug in cases of disease.

Unfortunately, our knowledge of its physiological action is most limited, and until very recently it has been almost entirely confined to the original studies made upon animals by the investigators just named.

Heat Functions.—Fortunately for our knowledge of the influence of phenacetine upon heat functions, Ott,[2] of Easton, Pa., has carried out and published an apparently thorough research upon this question, and, as the calorimeter was used, his conclusions may be accepted as correct.

As a result of these studies we now know that phenacetine lowers febrile temperature by decreasing heat production with an accompanying decrease in heat dissipation. That these results are due to an action upon the nervous heat-centres is proved not only by our physiological knowledge, but by the fact that the febrile process was produced by puncture of these centres, and that no change occurs in the blood-pressure, under the influence of the drug, to account for any vasomotor palsy, with resulting loss of heat.

Circulation.—Upon the circulation phenacetine acts with comparatively little power, and it requires large doses to produce toxic effects.

[1] Centralblatt für die Gessammt Therap., April, 1887.

[2] Journal of Nervous and Mental Disease, p. 598, 1888.

In the following tracings (pages 116*a* to 116*e*) this is very evident, and it will be seen that even the largest dose given had no great effect upon the pulse-rate or blood-pressure, even though the amount used was exceedingly large when compared with the size of the animal. The same facts have been noted in man, and they are undoubtedly correct.

Blood.—When doses of from 15 to 30 grains of phenacetine are given to dogs, or any of the lower animals, the blood soon becomes darkened in hue, but no important symptoms seem to be produced. It has been proved by Hinsberg and Kast that this darkened blood is due to the presence of methæmoglobin, but they also assert that the spectrum band of this altered compound is often absent on examination, even though the blood be dark. The reason for this absence is easy to discover when we remember that the spectrum of methæmoglobin does not appear unless this compound is present in excess, and, as a consequence, only very large doses of phenacetine can produce it in sufficient amount to be spectroscopically recognized. The very fact that the drug is so closely allied to antifebrin shows it to be capable of producing methæmoglobin, and we can rest assured that, while phenacetine is harmless in its influence on the blood in ordinary quantities, in very large toxic doses it acts destructively upon this tissue of the body.

Nervous System.—The only studies of the physiological action of phenacetine upon the nervous system of animals with which the writer is acquainted are those which he has performed himself, an example of which here follows :—

Frog; weight, 3 ounces.

10.45. Gave 1 grain of phenacetine into posterior lymph-sac.

10.50. Became quiet and somnolent. Moved slowly on irritation. Reflexes somewhat heightened in activity.

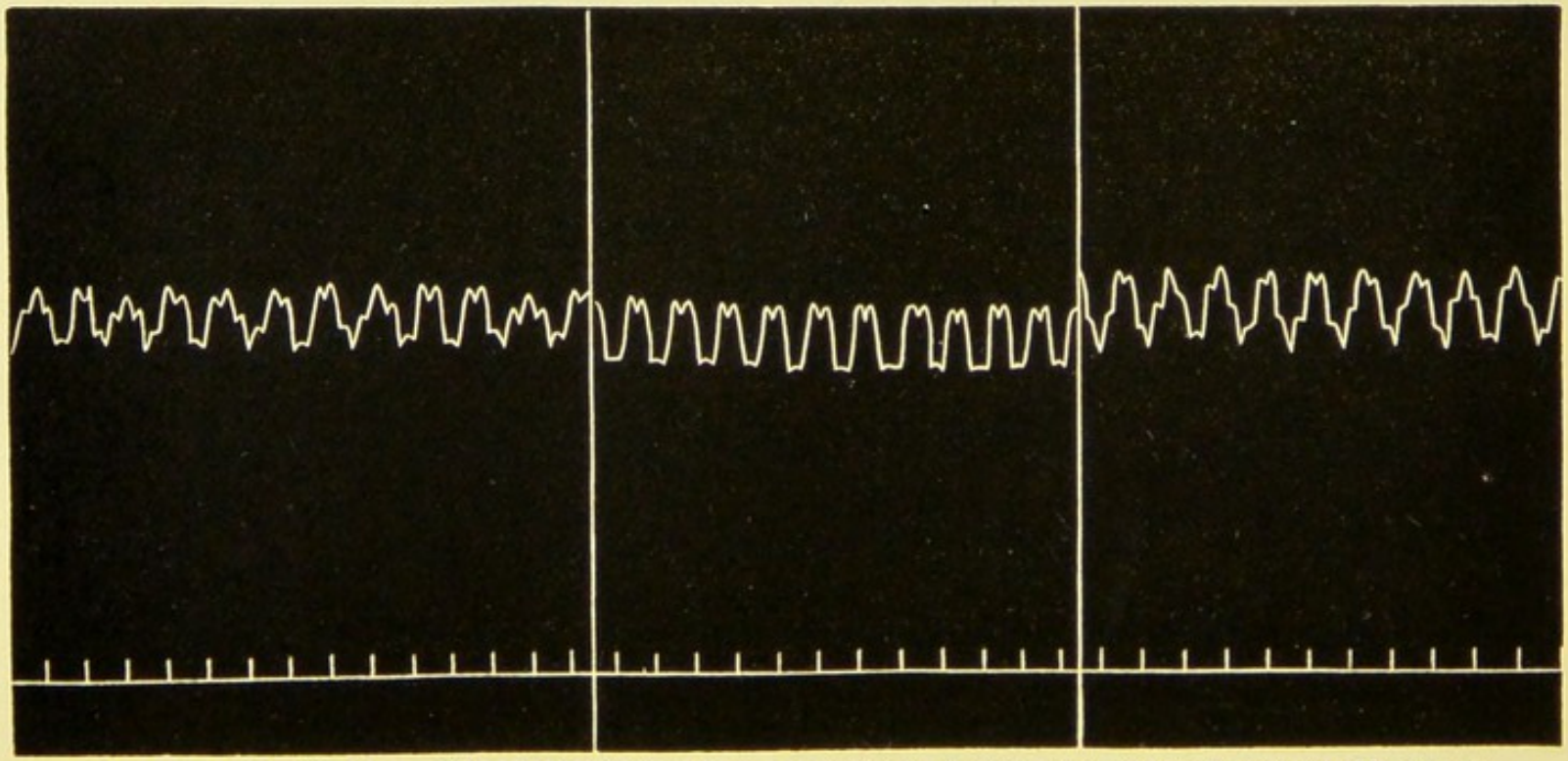
10.52. Reflexes are decreased. Blood is dark and venous-looking. Skin on inside of thighs is discolored. Animal breathing very faintly.

10.58. Dead from respiratory failure. The heart gives sometimes an abortive beat.

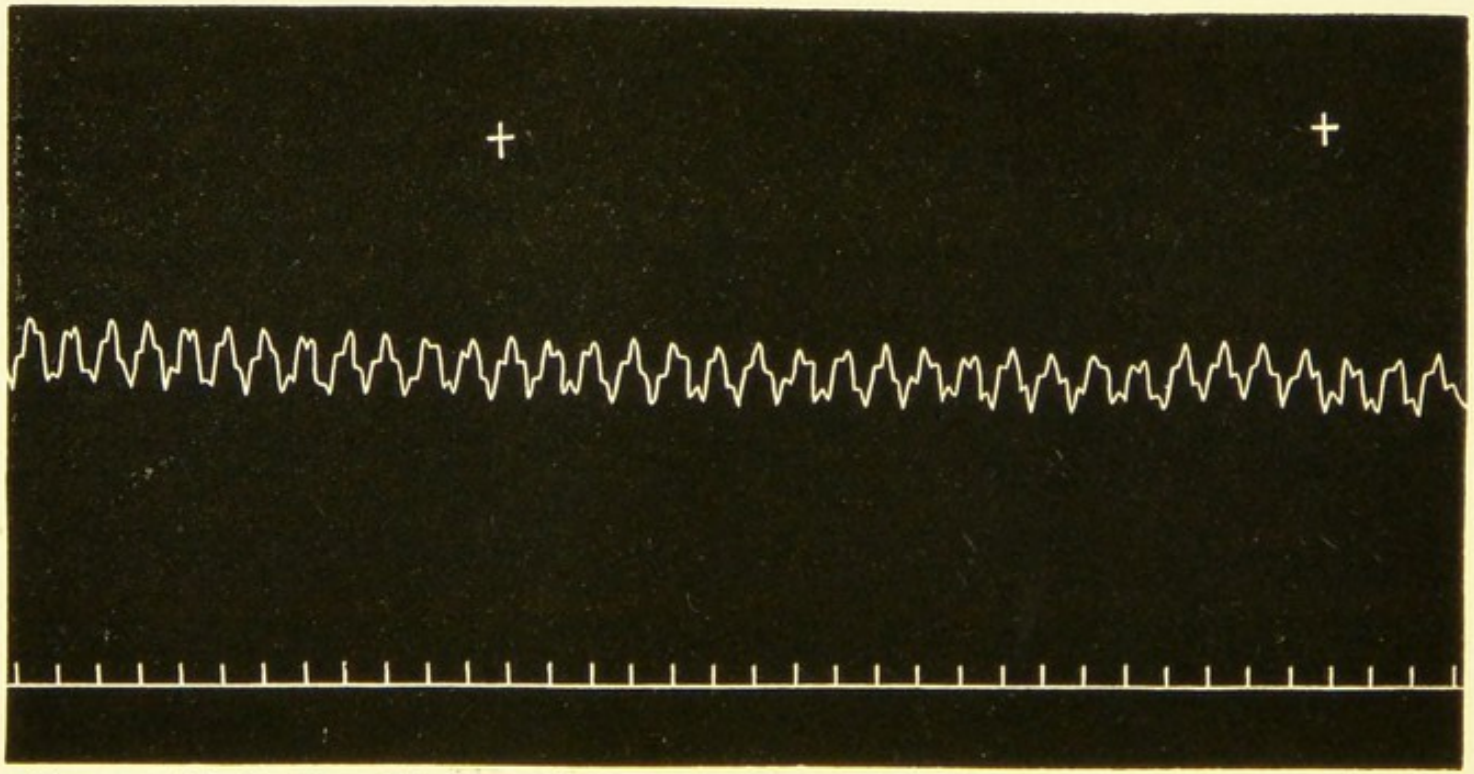
In order to determine the cause of the loss of reflex action noted in this and similar experiments, other frogs were now given doses of the same size, the artery of the left leg being tied to protect that member. The same symptoms ensued as before, and the protected leg seemed as much affected as the unprotected limb, pointing to the spinal cord as the part affected. This was further confirmed by the injection of a small amount of the drug into the leg of the frog, the blood-vessels being tied. It was then found that this limb responded as well to stimulus as the other, proving that the nerve-trunks were unaffected, and that the failure of reflex activity must be spinal in origin.

The increase of reflex activity noticed at first depends solely upon an indirect action of the drug upon the cord, and not upon a direct effect; that is to say, the primary increase of reflex activity is due to the changes in the blood, and not to an effect directly exercised upon the nervous protoplasm. That the sensory side of the spinal cord is more affected than the motor, is proved by clinical as well as experimental observation.

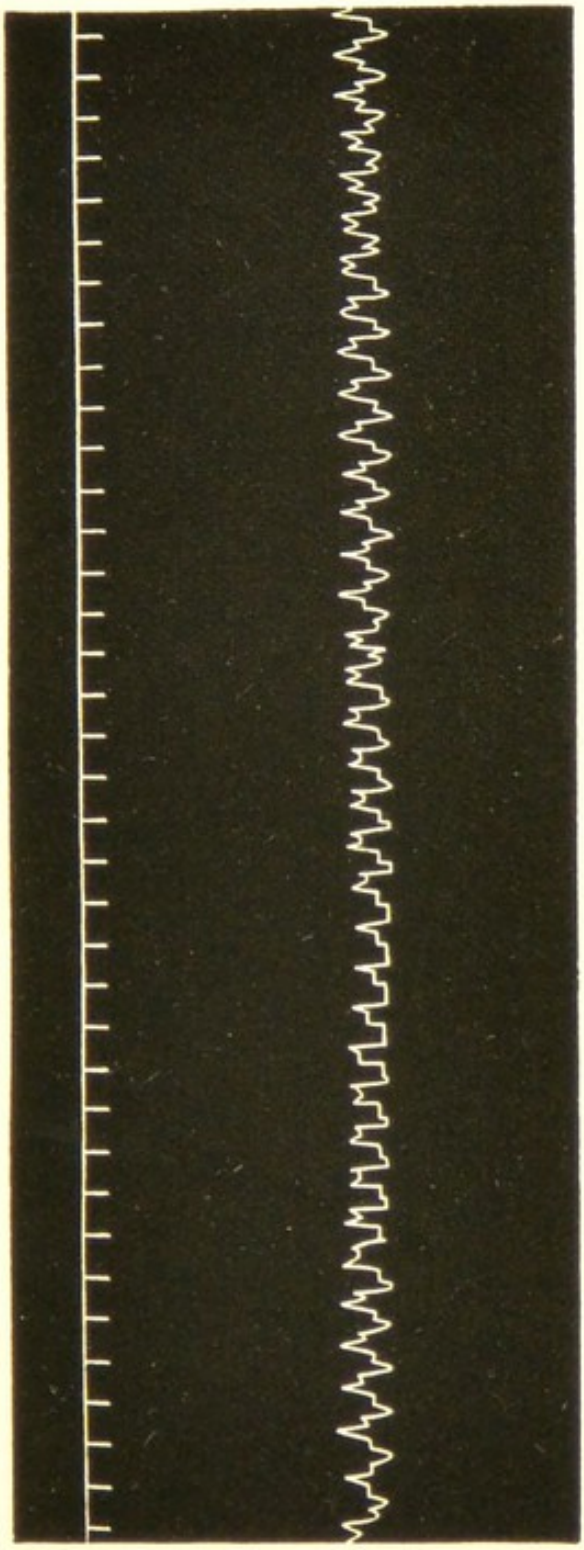
Urine and Elimination.—When as much as 45 grains of phenacetine are given to a dog the urine becomes strongly yellow, but not particularly dark; and it has been found by Hinsberg and Kast that chloride of barium shows no sulphuric acid, but that boiling with



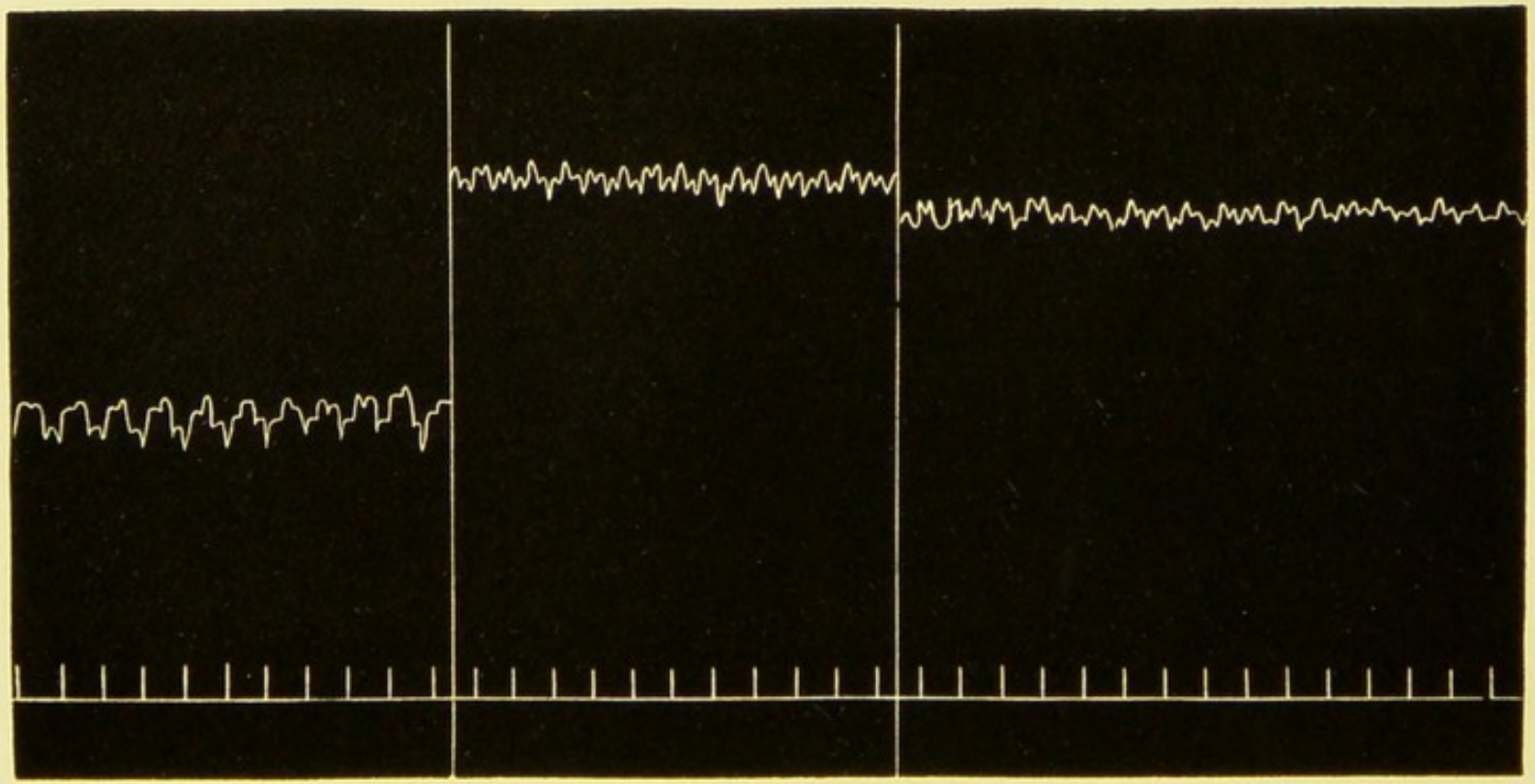
TRACING NO. 1.—DOG: WEIGHT, 20 POUNDS. INJECTED 3½ GRAINS INTO JUGULAR VEIN IN FIRST SECTION, EACH SECTION TWO MINUTES APART.



TRACING No. 2.—DOG; WEIGHT, 16½ POUNDS. INJECTED INTO JUGULAR VEIN 7 GRAINS IN 20 C.CM. OF WATER AND GLYCERIN BETWEEN + MARKS.



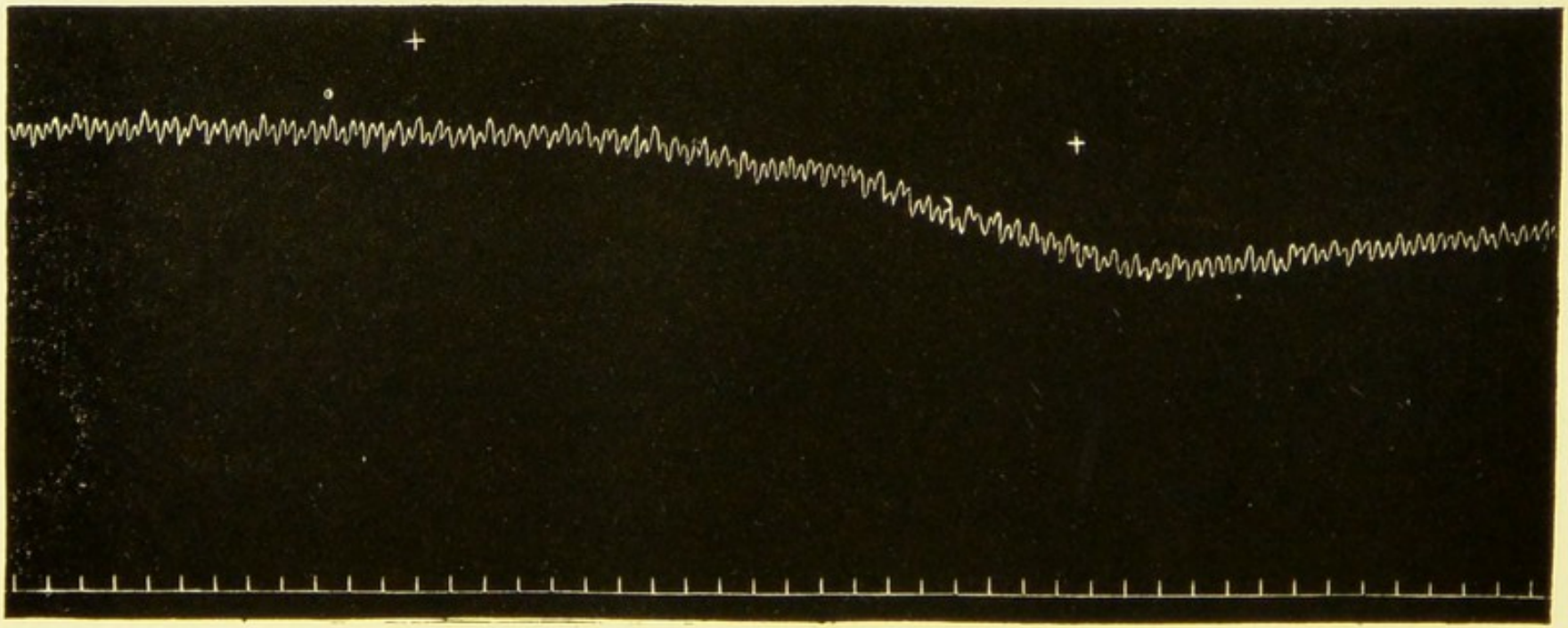
SAME CONTINUED. NO BREAK IN TIME.



SAME CONTINUED, TWO MINUTES LATER.

SAME CONTINUED, THREE MINUTES LATER.

SAME CONTINUED, FOUR MINUTES LATER; BLOOD VERY GRUMOUS.



Tracing No. 3.—Dog; Weight, 12 Pounds. Very Large Dose, 15 Grains, into Jugular Vein Between + Marks. More than a Grain to the Pound.

hydrochloric acid gives a copious precipitate of salts, which, accordingly, must exist exclusively in paired conditions or combinations. Copper oxide, when added to such urine, is reduced by prolonged boiling, and it has also been found that the urine rotates light half a degree to the left.

Müller[1] asserts that the addition of a solution of perchloride of iron produces with such urine a reddish-violet hue.

The use of phenacetine in man, however, seems to cause a dark-yellow color of the urine, and the indophenol reaction can readily be obtained after 9 grains of the drug are given.

A very important point, from a clinical stand-point, is the fact that this urine often gives the reaction for sugar with Fehling's solution, and for this reason the physician should be on his guard, lest he be led into a mistaken diagnosis of diabetes.

Toxic Effect.—The toxic effect of phenacetine is only produced when very large amounts are used.

Dujardin-Beaumetz[2] states that he has given as much as 37½ grains to a rabbit of 5 pounds without any toxic effect, and Misrachi and Rifal[3] also gave to a chicken 18 grains without any signs of poisoning. They have also given 30 grains to animals for every 2 pounds of body-weight without bad effects.

Conclusions as to Physiological Action of Phenacetine.—1. Phenacetine lowers normal temperature, and in fever lowers the pyrexia by decreasing the production and dissipation of heat.

2. Upon the heart and circulation the drug has a very slight influence.

[1] Berliner klin. Wochenschrift, No. 30, p. 613.
[2] British Medical Journal, March 9, 1889.
[3] Bull. Gén. de Thérap., June, 1888.

3. Enormous toxic doses cause the blood to become dark and grumous, and change the hæmoglobin into methæmoglobin.

4. On the nervous system the drug exerts a distinct quieting influence by depressing the spinal cord, particularly on its sensory side.

5. The urine may become dark yellow under its influence, and cause a reaction with Fehling's solution.

6. How the drug is eliminated we do not know.

Clinical Evidence.

Our knowledge concerning the influence of phenacetine upon the human body in disease may be divided into two separate parts, in much the same manner that we divided the discussion of antipyrin, namely, its use as an antipyretic and as an analgesic.

Like the other members of the antipyretic group which are blessed with this double action, the antipyretic influences of phenacetine were first observed, and will, therefore, be spoken of before its analgesic powers are considered.

The employment of this drug in medicine was first attempted by Hinsberg and Kast,[1] who, from the beginning, spoke of it in the highest terms of praise. They found that it seldom, if ever, caused serious untoward effects, and that its power over fever in the dose of from 3 to 8 grains was quite extraordinary. Very shortly after the paper of these writers appeared, Kobler[2] published the report of its use in some 50 cases in the clinic of Bamberger, of Vienna, the febrile affections being tuberculosis, pneumonia, typhoid fever, pleurisy, and several other diseases of like character. He found, as

[1] Centralblatt für die Wissenschaften, No. 9, 1887.

[2] Wiener Med. Wochenschrift, 1887; or Centralblatt für die Gesammte Therapie, August, 1887.

have most of his successors, that the fall of fever does not occur for nearly half an hour after the dose is taken, and continues for from four to eight hours afterward.

As a general rule, sweating was not noted as being present to any great extent, but in phthisis and advanced typhoid fever there can be no doubt but that chilliness and subnormal temperature may be caused. Cyanosis and vomiting did not occur in a single one of Kobler's cases. In a very instructive case of pneumonia, due to septic infection in a patient of 20 years, phenacetine not only lowered the fever, but, in addition, decreased, to a large extent, the blood in the urine, and did not, in the slightest degree, influence the kidneys unfavorably. That the drug has power is evidenced by the fact that Kobler used it only when the temperature rose as high as 103°, 104°, or 105° F., and in these cases the temperature fell not less than from 3 to 5 degrees.

It is very important to remember that morning doses of phenacetine seldom have as powerful an influence as evening doses. Two morning doses are only equal to one evening dose in most cases, and it is generally found better in phthisis to give the drug about noon, to prevent the evening exacerbation of temperature than to resort to it at a time nearer the pyrexial period. These conclusions of Kobler have been confirmed by Heppe[1] in a long series of studies, and the latter also points out the deleterious excess of apyrexia which sometimes comes on in debilitated cases of phthisis which take the drug.

One of the advantages of having several drugs belonging to one class is the benefit often derived from the use of one where another has failed. Thus, Huber[2]

[1] Therapeutische Monatshefte, April, 1888.
[2] Correspondenzblatt für Schweizer Aerzt, No. 18, 1888.

found that in several instances phenacetine was successful where antipyrin had not acted, and believes it to be the more powerful drug of the two,—a conclusion also reached by Heusner,[1] who thinks that 15 grains of phenacetine are equal to half as much antifebrin and to 30 grains of antipyrin. Lepine,[2] who has done so much with the other antipyretics, also believes it to be superior to them all, and in this Guttmann[3] is largely of the same opinion. Similar results to those so far named have also been reached by Gueorguievski,[4] Misrachi and Rifal,[5] Suckling,[6] Mays,[7] Roe,[8] and Rumpf,[9] as well as Greenfell,[10] Müller,[11] Zannas,[12] Perera, Pesce,[13] and Cesari and Burrani.[14]

One of the most thorough and careful studies, other than those which have been named, is that of Cattani,[15] of Milan, who has used phenacetine in over 50 cases of all kinds, and whose conclusions are well worth reading. He found that not only does phenacetine readily reduce pyrexia, but also that it acts more favorably when the fever is high than when it is low, and that the arrival of the temperature at the normal is not accompanied by the evil after-effects so often observed with other antipyretics.

[1] Therapeutische Monatshefte, p. 103, 1888.
[2] La Semaine Médicale, December 21, 1887.
[3] Deutsche Medicinal-Zeitung, July 12, 1888.
[4] Bulletin Gén. de Thérapeutique, May 30, 1888.
[5] *Ibid.*, June 15, 1888.
[6] British Med. Journal, April 28, 1888.
[7] Medical News, August 20, 1887.
[8] British Medical Journal, May 26, 1888.
[9] Berliner klin. Wochenschrift, June 4, 1888.
[10] Practitioner, May, 1888.
[11] Therapeutische Monatshefte, August, 1888.
[12] Gazette Méd. de l'Orient, June 30, 1888.
[13] Le Bulletin Médicale, May 30, 1888.
[14] Bulletin Gén. de Thérapeutique, June 15, 1888.
[15] Gazetta Medica Italiana Lombardia, 1888, Nos. 39 to 48.

Faulkner,[1] of the Bombay Army, has studied phenacetine, and he finds in most instances that its action is most favorable in the pyrexia of malarial affections. He concludes that in phenacetine we have a most useful medicine in the treatment of cases so commonly seen in India and other tropical countries, namely, those intermittent and continuous fevers which sometimes act with surprising rapidity and violence both as to their temperature and systemic influence. He thinks that though phenacetine does not always act in proportion to its dose, no disagreeable effects follow its employment whatever, even though larger doses than necessary are used. Rohden[2] has come to a similar opinion, but Warfringe[3] has denied the correctness of this belief. It has also been found that in typhoid fever, while the drug does not cure, it successfully combats the fever, diminishes the headache, and clears the mind. In croupous pneumonia the drug lowers the fever, but does not alter the course of the disease, although it diminishes the pain and relieves the dyspnœa.

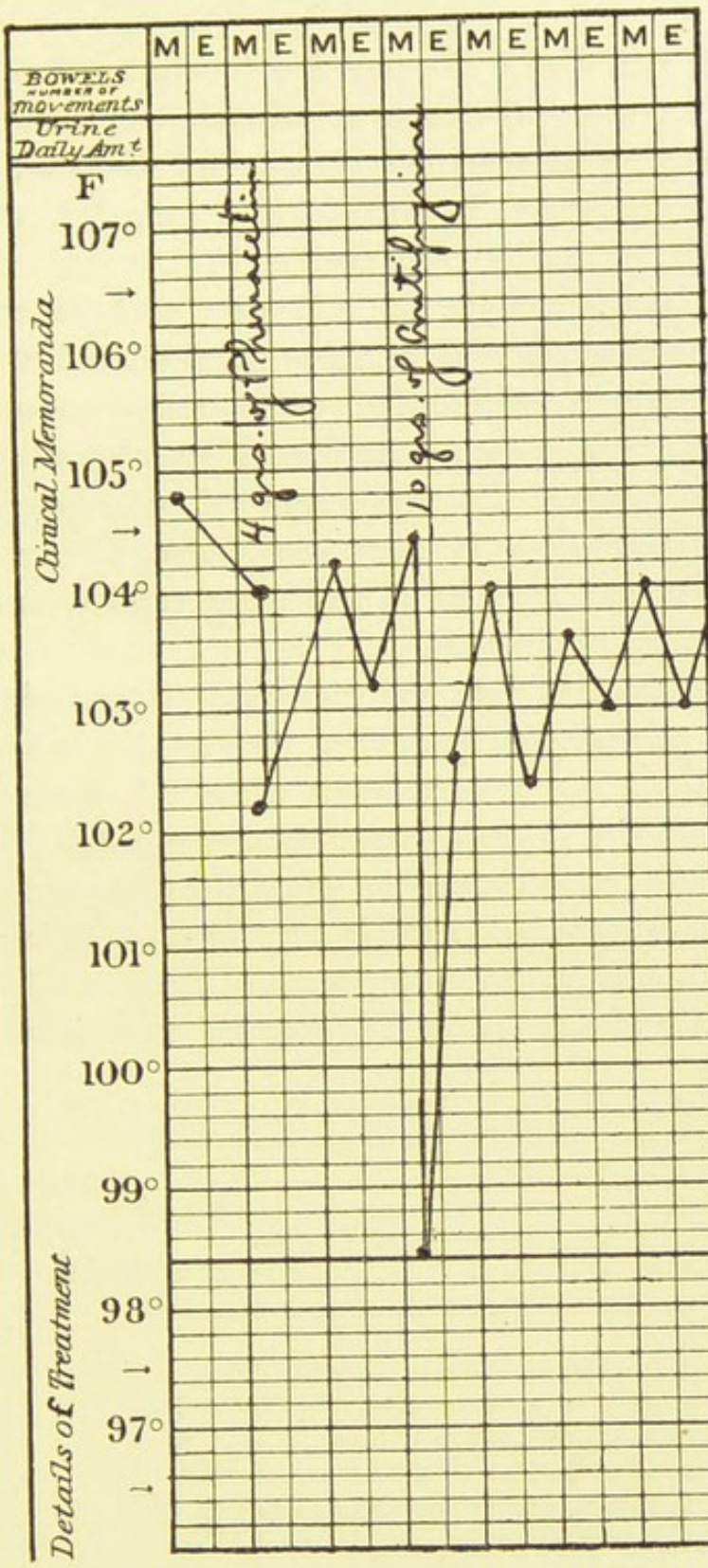
The conclusions which the writer has reached are identical with those named above. He has found the drug to be possessed of powerful antipyretic influence, and to be useful in nearly all the fevers in which antipyrin can be employed. At the same time, he does not look upon it with the same degree of confidence that he does the older drug, when he is anxious to relieve a fever which seems dangerous and worthy of rapid and certain reduction.

Nervous System.—Among those who have found phenacetine of value in the treatment of pain may be

[1] Indian Medical Gazette, August, 1889.
[2] Deutsche Medicin. Wochenschrift, May 3, 1888.
[3] Hygeia, Stockholm, August, 1888.

UNTOWARD EFFECTS OF ACETPHENETIDIN.

AGE.	SEX.	DOSE.	TIME OF ONSET.	SYMPTOMS.	DURATION.	RESULT.	BY WHOM AND WHERE REPORTED.	TEMPERAMENT.	DISEASE.	REMARKS.
Adult.	F.	9 grs. at one dose.	In an hour or two.	Body covered with red spots, particularly the extremities; urine was dark.	1 day.	Recovery.	VALENTIN. Therap. Monatshefte, July, 1888.	Nervous.	Anæmia, sleeplessness, and headache.	
22	F.	5 grs. at one dose.	In a few hours.	Body covered by large wheals, as if from hives.	1 day.	Recovery.	Seen by myself.	Nervous.	Typhoid fever.	
31	M.	5 grs. t.d.	After third dose.	Body covered by raised wheals, somewhat reddened.	12 hours.	Recovery.	Seen by myself.	Phlegmatic	Typhoid fever.	



TEMPERATURE CHART SHOWING THAT ANTIPYRIN IS MORE POWERFUL IN REDUCING FEVER THAN PHENACETINE.

named Ott,[1] Müller,[2] Heppe,[3] Hottenstein,[4] Pesce,[5] Cesari and Burrani,[6] Guttmann,[7] Michaelis,[8] Gueorguievski,[9] Rumpf,[10] Heusner,[11] Zadok and Nessim,[12] Misrachi and Rifat,[13] Dujardin-Beaumetz,[14] Preston,[15] Rabuski,[16] Cattani, [17] and Gaiffe.[18]

As an antineuralgic, in migraine and in ordinary headache from eye-strain, in tabes dorsalis, in intercostal neuralgia, and in rheumatism, phenacetine undoubtedly brings relief very rapidly, and does so even when antipyrin has failed. In the acme of whooping-cough Michaelis has seen it take the place of antipyrin. Indeed, it would seem as if the drug rivaled antipyrin in its nervous influences.

Gaiffe found it relieved the pain of gastralgia and did good in nervous polyuria. Thus, in a case of the latter disease, the excretion of urine fell under phenacetine from 215 ounces to 140 ounces per day.

The following words of Dujardin-Beaumetz seem worth repeating here without any excuse being made for their interpolation, and, coming from such a distinguished French writer, are worthy of consideration.

[1] Prager Medicin. Wochenschrift, October 3, 1888.
[2] Therapeutische Monatshefte, August, 1888.
[3] *Ibid.*, April, 1888.
[4] University Medical Magazine, January, 1889.
[5] Le Bulletin Médicale, May 30, 1888.
[6] Bull. Générale de Thérapeutique, June 15, 1888.
[7] Deutsche Medicinal-Zeitung, July 12, 1888.
[8] *Ibid.*
[9] Bull. Gén. de Thérap., May 30, 1888.
[10] Berliner klin. Wochenschrift, June 4, 1888.
[11] Therapeutische Monatshefte, p. 103, 1888.
[12] Gazette Méd. de l'Orient, June 30, 1888.
[13] Bull. Gén. de Thérapeutique, June 15, 1888.
[14] British Medical Journal, March 9, 1889.
[15] American Medical Digest, April 15, 1889.
[16] Deutsche Med. Wochenscrift, No. 37, 1888.
[17] Gazetta Medica Italiana Lombardia, 1888, No. 39.
[18] Bulletin Générale de Thérapeutique, 1888, p. 71.

"But it is above all as an analgesic that phenacetine outrivals its predecessors. While it is quite as powerful as antipyrin and acetanilid, it does not cause the pain in the stomach, or the scarlatiniform rash of the former; nor does it give rise to the cyanosis of the latter. However prolonged may be its administration,—and I have given it for months in doses of 1 to 2 grammes (15 to 30 grains) per day,—I have never observed any bad effect. I have used it for the relief of every form of pain (neuralgias, migraine, rheumatic pains, muscular rheumatism, acute articular rheumatism, the lightning pains of tabes, etc.), and always with the best results. Further, in cases of hysteria, and of hysterical or neurotic pains, phenacetine has seemed to produce better effects than the bromides; it calms the excitability of the nervous system, and in some obstinate cases of nervous insomnia it produced sleep. Phenacetine seems, therefore, to be not only an analgesic, but a narcotic."

The results of the writer's trials of phenacetine in the wards of the St. Agnes Hospital are entirely confirmatory of these opinions, except in so far as any narcotic effects are concerned.

The two following cases illustrate the activity of the drug in relieving pain:—

Case 1.—A. O., aged 48 years; laborer. Suffers from chronic myelitis and much pain about small of back. Sometimes has "girdle-pains" of a severe character, which last for a week at a time.

Ordered 4 grains of phenacetine three times a day, with an almost complete relief from the pain. Antipyrin did no better, but as well, for him.

Case 2.—B. E., male; laborer; also suffering from chronic myelitis, with pain in the lumbar region and

"girdle-pains." Two grains three times a day relieved him completely, and the dose was first reduced to twice a day, and then to one dose at night. Of course, the progress of the disease was not checked.

SALICYLIC ACID AND ITS COMPOUNDS.

Originally introduced into medicine for the purpose of acting as an antipyretic, salicylic acid is rarely employed for that purpose to-day, being almost solely used for its antirheumatic power. That the drug does possess antipyretic influences to some extent has been proved over and over again, but it has also been found that, compared with the newer antipyretics, it is very weak.

While the propriety of considering the drug as an antipyretic may be questioned, the writer has done so because it seems best to include the good and the bad, in order that the distinction may be the more marked.

Experimental Evidence.

General Effects.—When salicylic acid is given in sufficient dose to a normal man it produces a condition of ringing in the ears closely resembling that caused by large doses of quinine. If this symptom is not present it may be replaced by buzzing or bell-like sounds, or loud reports quickly following each other. The face may be somewhat flushed and the eyes slightly blood-shot. If the dose used be still larger, these symptoms are naturally much increased. The ringing in the ears goes on to total deafness and dimness of vision; amblyopia of a complete type and profuse sweating and exhaustion may assert themselves, and the temperature of the body is usually subnormal.

The symptoms just detailed are those of large, non-toxic doses, and do not include those seen in truly poisoned patients. In this class the amblyopia is fol-

lowed by ptosis, more or less marked, by wild, incoherent delirium, of either a melancholic or cheerful type, and by irregular respiratory movements. By and by, the delirium becomes more quiet and the patient or animal slips gradually into a coma, from which nothing can arouse him. The pulse is now slow and weak, or fluttering in its powerlessness, the urine is passed, along with the fæces, involuntarily, and is of a peculiar, greenish hue, pathognomonic of the presence of the drug. The cause of this color will be spoken of later on. In dogs death ensues amid convulsions and dyspnœa, the fatal result being brought about by failure of respiration.

Heat Functions.—The administration of salicylic acid to an animal having a normal temperature nearly always has the effect of lowering the heat of the body a fraction of a degree at least. Not only has the writer found this to be the case in man, but in animals also, and in this he is confirmed by a large number of other investigators both in this country and abroad.

The following experiment represents fairly well the results reached by me in several experiments on rabbits.

Experiment.—Rabbit; weight, 3 kilos; gray; full grown.

10.35.	Rectal temperature, ...	102.5
10.40.	Gave hypodermically 2 grains of salicylic acid.	
10.45.	Rectal temperature, ...	102.5
10.50.	" "	102.4
10.55.	" "	102.25
11.05.	" "	102.1
11.15.	" "	101.8
11.25.	" "	101.3
11.35.	" "	101.3

Confirmatory of these experiments are those of Gedl,[1] North,[2] Chirone and Petrucci,[3] all of whom

[1] Centralblatt für die Med. Wissenschaften, 1876, p. 403.

[2] Practitioner, xxiii, 184.

[3] Commentario Clinica di Pisa, January and February, 1878.

state that moderate doses of salicylic acid lower normal bodily temperature. It is true that in Gedl's experiments upon man the result was not constant in every case, but the changes noted by North were very marked indeed, for he found that the drug absolutely prevented the rise of bodily heat usually consequent upon severe muscular effort. The experiments of the writer were all performed on rabbits in perfect health to the number of five, and showed a constant fall of temperature amounting to a fraction of a degree or more. Using dogs and rabbits, Chirone and Petrucci also found such a fall to occur.

The effect of larger, almost toxic, doses of the drug upon temperature in health is not constant, and it is this which has given rise to the assertions made by some writers that the temperature was not depressed by salicylic acid, but even raised. That these statements are based upon accurate observation cannot be gainsaid, but it will be found on examination of the papers that the doses employed by all were not the same. Chirone and Petrucci recognize this fact, and state that poisonous amounts may raise the bodily heat rather than lower it, and in this they are confirmed by the results of Germain Sée,[1] who found that as much as 150 grains had little if any depressing effect. Aside from this, it is but fair to state that Danewski found the action of ordinary amounts identical in the dog and man, and that Furbringer,[2] in a similar line of investigation, reached corresponding results. In view of the studies of the writer, whose animals were free to run about, and, in view of those of Gedl and North, it is justifiable to reach the conclusion that, while the action of salicylic

[1] Bulletin de l'Académie de Médecin, June, 1877.

[2] Centralblatt für die Med. Wissenschaften, November 18, 1875.

acid on normal temperature is not always constant, the tendency of small doses is to act as a depressant.

The manner in which this fall occurs is not positively known, and is difficult of discovery owing to the small variation produced; but the writer, in a series of studies, came to the conclusion that it resulted from decreased heat production and dissipation. He believes, however, that this conclusion is not to be taken as entirely correct, since his results hardly support his deductions, owing to the slight fall which ensued after the doses which were used.

Upon the fevered animal the drug always tends to act as an antipyretic, as has been proved a great number of times by clinicians and experimenters. Thus, Furbringer produced septic fever in rabbits, and found in 9 cases a distinct lowering of the temperature after the administration of the drug, the dose varying from $\frac{1}{2}$ to 3 grains. The fall occurred in from four to six hours after the drug was given. The same results were also reached by him in the case of two rabbits who were fevered by a pyæmia due to the injection of pus under their skin. On other animals who were fevered by inunctions of croton-oil the drug had little effect.

The writer has found, however, that small doses have no influence over the fever produced in dogs by the injection of pepsin, probably because his doses were too small. His calorimetrical experiments on this question are of little value owing to this fact, but, so far as he can judge, the fall is due to diminished heat production and dissipation.

Zimmermann[1] found, in some experiments on rabbits carried out in the Pharmacological Institute of Greifswald, in which fever had been produced by the injec-

[1] Archiv für Experimental Pharm. und Pathologie, 1875, p. 248.

tion of putrid substances, that salicylic acid, given by the mouth or subcutaneously, produced virtually no antipyretic effect.

Circulation.—Our knowledge of the influence of salicylic acid on the circulation has been in the past confused and uncertain, and the writer has, therefore, thought it well to perform a number of experiments in regard to these points, the results of which may be seen in the following tracings (pages 132*a* to 132*d*).

From these it would appear that in moderate amount the drug does not depress the pulse-rate or arterial pressure, but if, by chance, it comes in contact with the heart in large amounts or very suddenly, it depresses that viscus. This is confirmed by the assertion of Chirone and Petrucci, namely, that in the frog the heart-beats are diminished somewhat, while in the mammal they may be unchanged, or slowed, or accelerated.

Further than this, Oltremare[1] has found that the drug increases the arterial pressure and pulse-force, as has also Danewski.[2] The rise of pressure noted by them was due to stimulation of the heart and vasomotor centre, for the rise did not occur if previous section was made of the spinal cord. The author has confirmed these studies, as may be well seen in the tracings.

When a dose amounting to 2 grains is injected into the jugular vein of a dog of 21 pounds, there is a fall in pressure and pulse-rate of a very marked degree. This has been confirmed by Kobler,[3] and also by Oltremare and Danewski, who have found that the action is exerted directly upon the heart.

Although tracings taken from the surface of a blood-

[1] Thèse de Paris, 1889.

[2] Arbeiten d. Pharmacol. Laborat. Moskau, i, 190.

[3] Centralblatt für die Med. Wissen., 1876, pp. 163, 195.

vessel can be made to show almost anything, and are, therefore, not of much value, it is proper to notice here the studies of Maragliano[1] with the sphygmograph, who also used the sphygmomanometer of Basch upon patients under salicylic acid. He asserts that his results showed a rise of blood-pressure and pulse-force whenever the drug was used in moderate quantity.

Tissue Waste or Bodily Metabolism.—The knowledge which we possess in regard to the influence of salicylic acid or its compounds upon the tissues of the body is, to say the least, meagre. The most reliable information is that of Wolfsohn,[2] who has found that under its influence the nitrogenous elimination is considerably decreased. On the other hand, Germain Sée[3] states that in gout the uric acid thrown off by the body is very greatly increased and the quantity of urea remains unaffected,—a result which, if correct, is, to say the least, curious and inexplicable.

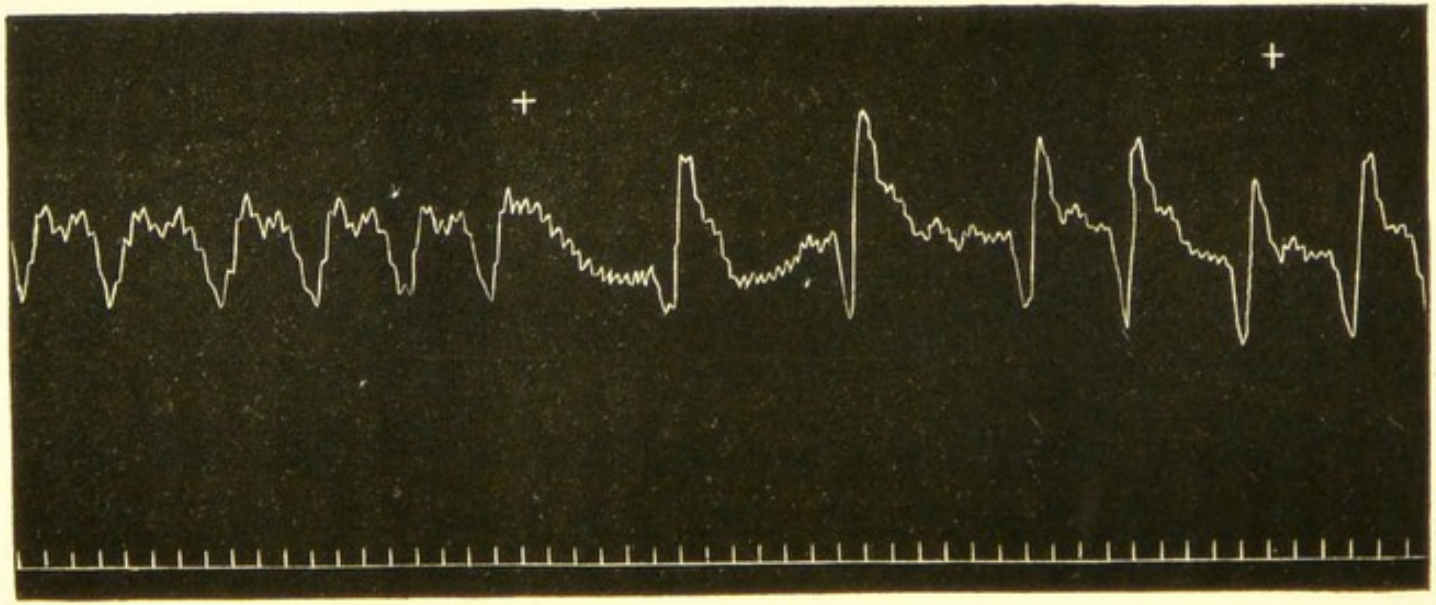
The studies of Lecorche and Salamon upon patients suffering from rheumatism show a primary increase of great extent in the excretion of urea and uric acid, followed by a diminution which, in its fall, may pass below the line maintained before the drug was used. Thus, they found that in acute rheumatism the increase lasted three or four days; in subacute rheumatism one or two days, with an excretion of phosphoric acid, which was at first increased, then lessened. These results have also been largely confirmed by Carl Virchow,[4] who, in using dogs, found the nitrogenous elimination increased by salicylate of sodium.

[1] Zeitschrift für klin. Med., 1884, viii, p. 248.

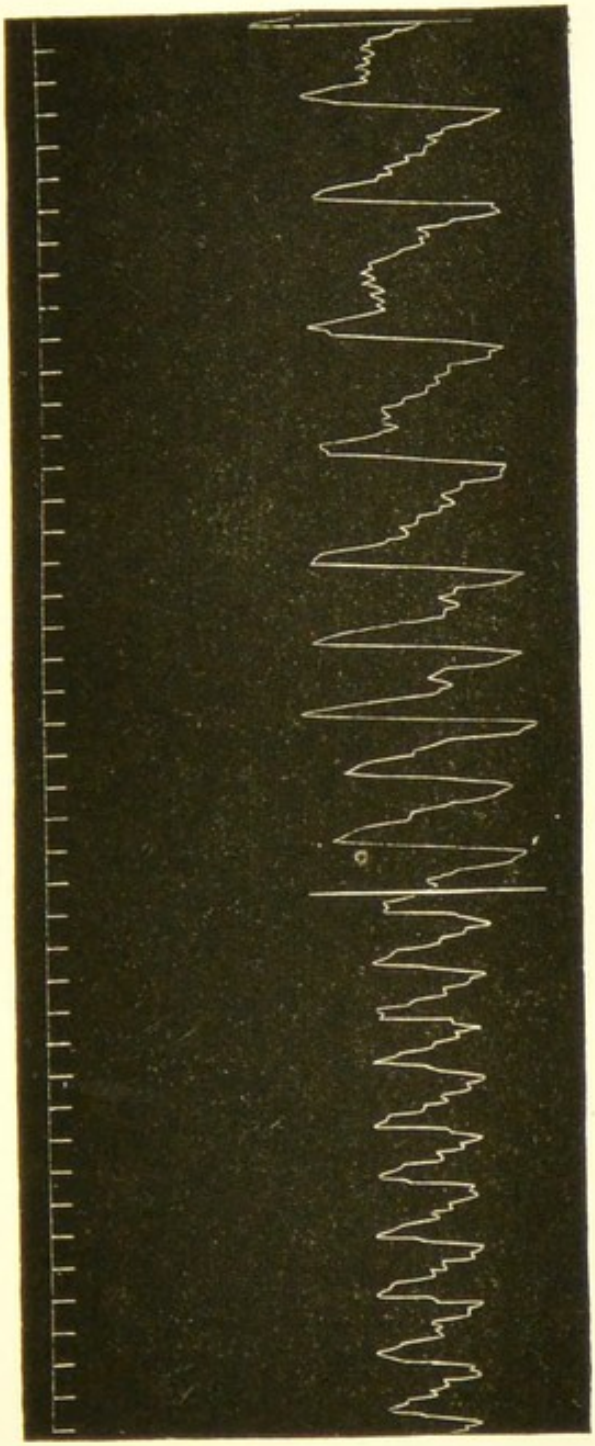
[2] Inaugural Dissertation quoted in Centralblatt für Medicinische Wissenschaften, 1877, p. 30.

[3] Bulletin de l'Académie de Médecin, 1877, p. 697.

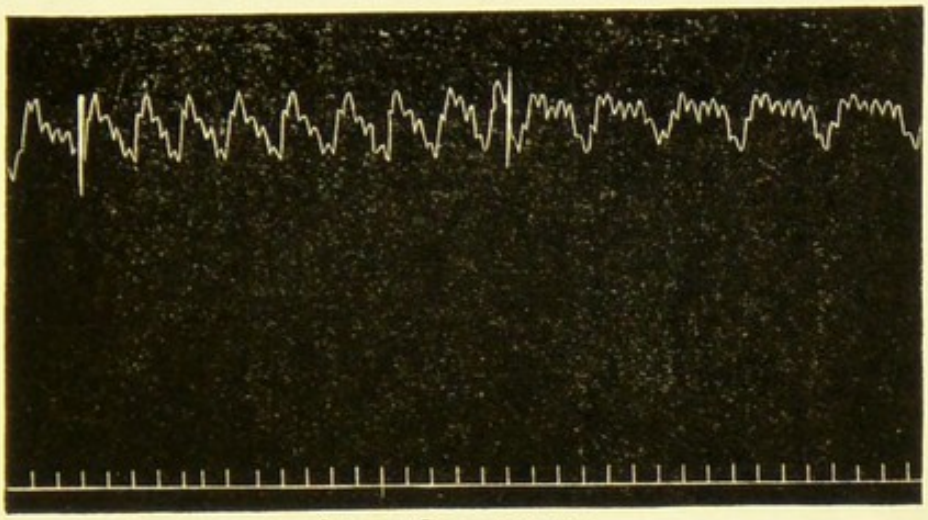
[4] Zeitschrift für Physiologische Chemie, vi, p. 78.



TRACING NO. 1.—DOG; WEIGHT, 40 POUNDS. INJECTED 2 GRAINS OF ACID BETWEEN + MARKS.



SAME CONTINUED.



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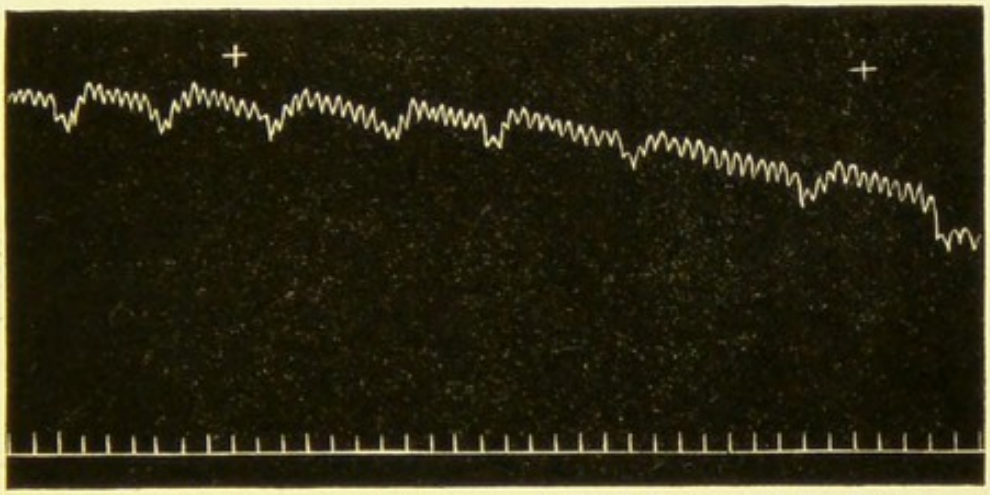
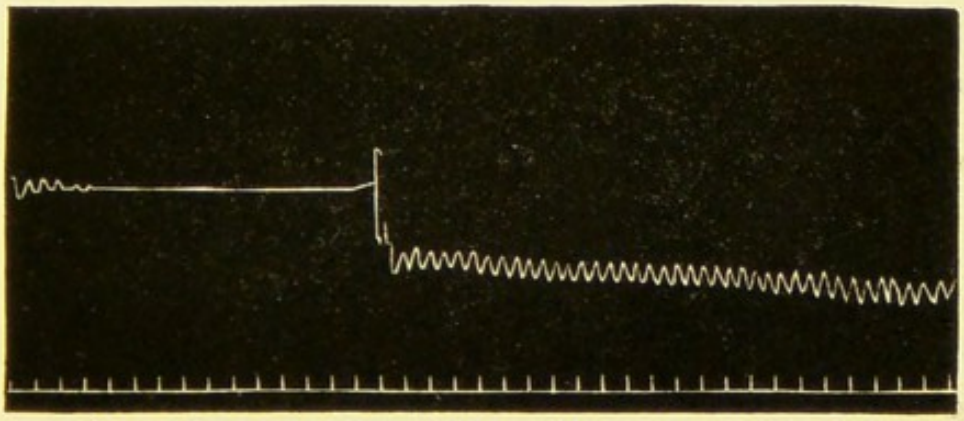
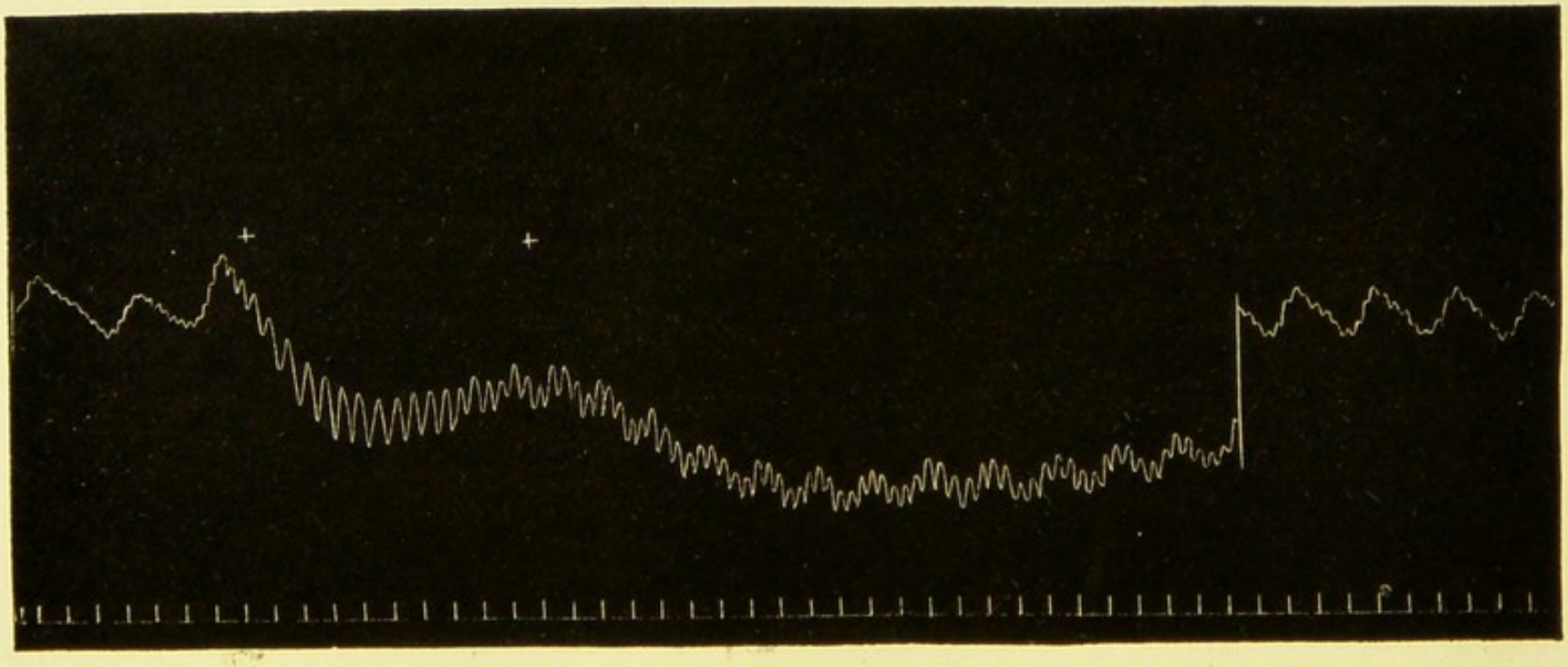


SAME CONTINUED. TWO GRAINS MORE GIVEN, WHICH CAUSED DEATH.



SAME CONTINUED, SHOWING APPROACH OF DEATH.



TRACING No. 2.—INJECTED 2 GRAINS OF ACID BETWEEN + MARKS, SHOWING THE EFFECT OF SALICYLIC ACID UPON THE CIRCULATION. THE HEART BECOMES LABORED IN ITS ACTION AS SOON AS A DOSE ENTERS IT SUDDENLY.

Nervous System.—That salicylic acid has quite a distinct influence over the nervous system cannot be denied, but that this influence in any way affects its value in fever or rheumatism is very doubtful. In the lower animals, after poisonous doses, violent clonic and tonic convulsions ensue, arising, apparently, both from the brain and spinal cord. The action on the nerve-trunks, both sensory and motor, seems to amount to nothing, and, unless the doses are quite toxic, no change in reflex action is apparent.

Laborde,[1] from studies on the dog, affirms that only the centres in the perceptive portions of the brain are affected, but admits that some of the spinal cells may also be depressed, and in this he is confirmed by the studies of Bochefontaine,[2] who found in frogs that the drug acted as a paralyzant of the spinal cord. It is at once evident that the convulsions witnessed by Sée are produced by larger amounts of the drug than caused the paralysis seen by Bochefontaine and Laborde; in other words, the coma of advanced poisoning was at such a time asserting itself, but yet enough of the drug had not been given to produce convulsive seizures. Laborde gave as much as 60 grains to a dog, and found cutaneous anæsthesia very well marked, but if he had given 120 grains he would subsequently, in all probability, have obtained a convulsive attack.

Respiration.—Here, again, most of our knowledge is derived from the studies of Kobler[3] and Danewski.[4] The first of these investigators noted that the drug, when injected into the jugular vein, caused a primary quickening of the respiratory movements, followed by

[1] Bulletin de Thérapeutique, xciii, p. 276.
[2] Le Progrès Médicale, 1877, p. 630.
[3] Centralblatt für die Med. Wissenschaften, 1876, p. 163.
[4] Arbeiten d. Pharm. Laborat. Moskau, i, p. 190.

a slowing which placed them below the normal rate. These conclusions have also been found correct by Danewski, who, with Kobler, found that section of the vagus nerves during the time the respirations were slowed caused a still further reduction in respiratory rate.

Danewski found, too, that if the vagus nerves were cut before any drug was given, the primary acceleration was almost absent. He concludes that the respiratory changes are reflex in character and dependent upon irritation of the terminal afferent filaments of the nerve in the pulmonary tissues. As to whether the drug affects the respiratory centre directly, we have no positive evidence.

Of two things, however, there can be no doubt: first, that even very large medicinal doses only affect the respiration but slightly, if at all; and, second, that poisonous doses in sufficient amount to kill do so by depression of the respiratory centre.

Absorption and Elimination.—Salicylic acid is absorbed very rapidly, indeed, by the body, whether it be in any of its combined salts or not. Not only is this true, but it is taken up with great rapidity by the skin and mucous membranes, and may even be administered to patients by applications to such surfaces. The writer has treated acute articular rheumatism on several occasions, when the stomach was disturbed, by inunctions of the acid rubbed up with vaseline; and Randolph has shown that the oil of gaultheria (salicylate of methyl) may be inhaled from a sponge and appear in the urine in a few minutes. The absorbability of the drug from the sound skin has also been tested and proved by Drasche.[1]

[1] Centralblatt für Chirurgie, 1876, p. 777.

Salicylic acid is so insoluble in ordinary menstrua that it is interesting to know how the digestive juices dissolve it, for, although they seem to possess great power as solvents, their action must be exceedingly rapid to enable the drug to appear in the urine so soon after its ingestion. At the present time, however, there exists little doubt but that salicylic acid is absorbed as such, and at once transformed into salicylate of sodium upon its entrance into the blood. This thought is not only confirmed by logical reasoning, but by the results reached by Salkowski,[1] which were of an identical character in their conclusions. Whatever of the acid escapes into the intestines probably is changed into a salt before it is absorbed by the alkaline juices there present.

Though this is the theory now most generally accepted, it is by no means that which has been universally received in the past. Very early in the study of the drug, Binz,[2] of Bonn, brought forth the theory that the acid is liberated in the blood by the carbonic acid there found, but his reasons for this belief are so poorly substantiated that they do not deserve more than a passing mention. He found that if carbonic-acid gas is passed through a solution of phosphate, carbonate, or salicylate of sodium, which is then agitated with ether and evaporated to dryness, crystals of salicylic acid appear. As has already been pointed out elsewhere, the same result ought to be obtained if the blood of an animal, poisoned by salicylic acid, be shaken with ether; but this is not so. Thus, Feser and Friedeberger found that only enormous (instantaneously) lethal doses would give such a result. Again, in a series of studies by

[1] Berliner klin. Wochenschrift, 1876, p. 297.
[2] London Practitioner, xxvi, 443.

Kobler,[1] upon this same point, it was found that no acid was yielded when poisoned blood was shaken with ether, unless that blood was venous in character, when, owing to the carbonic acid present, acid was yielded. It would seem probable, therefore, that the salicylic acid is not held, as is the case with quinine, in solution by the gases of the blood, but, by reason of its change in chemical form.

Feser and Friedeberger believe that the drug is held in solution as an albuminate, and Farsky[2] has confirmed this idea to some extent; at least, he succeeded in proving that the acid will form such a combination. This has been denied by Fleischer,[3] and, in consequence, the question as to this minor point is as yet undecided.

The studies which have been devoted to the determination of the manner of elimination of the acid, when once it is absorbed, have brought results at once more interesting and fruitful of general agreement. During the time that the question of the mode of absorption was worrying the minds of the physiological chemists, Furbringer and Drasche[4] found no trace of the acid in the fæces, saliva, bronchial secretion, or the sweat. Their conclusions have, however, been contradicted, probably correctly, by Mussy[5] and by Balz,[6] both of whom found the drug in the saliva. Outmont also found it in the serum of a blister.

It has been found that elimination by the urine is very rapid indeed, occupying only a few minutes, and the writer has confirmed the results of others on this point

[1] *Loc. cit.*
[2] Sitzb. d. k. Akad. d. Wissens., lxxiv, Bd. ii.
[3] Medic. Centralblatt, 1876, p. 628.
[4] Centralblatt für Chirurgie, 1876, p. 777.
[5] Bulletin Gén. de Thérap., xiii, p. 318.
[6] Archiv für Heilkunde, xviii, p. 60.

many times. Balz records an interesting case of exstrophy of the bladder, in which salicylicized urine was detected dripping from the ureters within 8½ minutes after the ingestion of the drug. Byanow[1] has recovered it from the urine in twenty-five minutes, and Ewald has seen similar cases. Any one can easily make studies upon himself by taking the drug and shortly afterward adding a few drops of a solution of the chloride of iron to his urine, when a purple hue will appear if salicyluric acid is present.

Aside from the rapidity of elimination we must examine as to the form of the drug when it escapes.

Byanow found it altered into salicyluric acid and salicin, and to a slight degree into oxalic acid. Stuart asserts that he has seen crystals of salicyluric acid in the urine even after small doses of the drug.

Whenever salicylic acid or one of its compounds is given in excess, the urine becomes olive-green in hue. This is said to be due to the presence of a chemical compound formed, not from the acid, but from its action with the juices and contents of the intestines. Aolfberg[2] and Robin[3] insist that this substance is indican, or pyrocatechin,[4] or that both compounds are present.

Antiseptic Action.—The antiseptic power of salicylic acid far exceeds that of most other antipyretics, yet it by no means holds a place equal to the drugs commonly used for such purposes. Acting in a much milder manner than carbolic acid or corrosive sublimate, it prepares so poor a field for the growth of micro-

[1] Centralblatt für Chirurgie, 1877, p. 809.
[2] Deutsche Archiv für klin. Med., xv, p. 403.
[3] London Med. Record, 1877, p. 151.
[4] Bulletin de l'Acad. de Méd., 1877, p. 507.

organisms that they fail to multiply. Its power is *antiseptic*, while the influence of the others is *germicidal.*

Aside from the abundant clinical proof which we possess, a large number of experimental studies, surrounded by all the accuracy of the laboratory, have been carried out. Very early in its use in medicine Kolbe found that four-hundredths of a 1-per-cent. solution prevented milk from souring to a very great extent, while Bucholz[1] has asserted that fifteen-hundreths of 1 per cent. will prevent the development of bacteria in ordinary organic mixtures. He also found so small a quantity as 0.005 per cent. to possess distinct power, while 0.3 per cent. killed bacteria which were previously in a flourishing state. Experiments on the salicylate of sodium showed it to be of almost equal value. Prideaux[2] has confirmed these results in a very practical manner in regard to urine, finding that ½ grain to the 1000 of urine keeps such a liquid clear for fourteen days, although very inactive bacteria can be seen in three days. One grain per thousand almost entirely inhibits any change, and 1½ grains render the urine capable of being kept indefinitely. He also found, what many others have noted, that the urine of patients taking this drug remains sweet for a long time. A rather curious fact is that the addition of 3 or 4 grains of salicylic acid to putrid urine kills all the bacteria, but does not in the least destroy the characteristic odor. Similar conclusions to those of Prideaux have been reached by Meyer and Kolbe,[3] and many others.

Further than this, Miller and Kolbe have found it to prevent the action of emulsin and amygdalin, so inhib-

[1] Arch. für Experimental Path. und Pharm., Bd. iv.
[2] London Practitioner, September, 1878, p. 177.
[3] Journal für Prakt. Chemie, Bd. xii.

iting the development of hydrocyanic acid. Miller also found the proteolytic ferment of pepsin seriously retarded in its action by the drug.

Conclusions as to the Physiological Action of Salicylic Acid and its Compounds.—Salicylic acid lowers normal bodily heat very slightly, but nevertheless seems to possess some such influence.

In fever it acts as a more or less powerful antipyretic according to its dose, the cause of the fever and its height.

On the circulation the drug has little effect in ordinary amounts, but if it comes closely in contact with the heart in concentrated form it acts as a paralyzant.

While the evidence in regard to its influence over tissue waste is somewhat contradictory, it would seem probable that in health and disease the nitrogenous excretion is increased, but afterward decreased. In very large poisonous doses it produces convulsions in the lower animals, preceded and accompanied by coma. The drug acts chiefly on the brain and spinal cord, not on the nerves and muscles.

Ordinary amounts quicken the respiration very slightly; larger ones kill by depression of the respiratory centre.

As an antiseptic it possesses very considerable power, but no germicidal influence.

Clinical Evidence.

That overdoses of salicylic acid are perfectly capable of producing serious effects has already been pointed out, and on the following pages the writer has collected a list of cases reported by various writers where patients taking the drug either had bad symptoms produced by overdoses, or had such an idiosyncrasy as to be equally seriously affected:—

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 1.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
20	F.	60 grs. in 2 doses; total, 120 grs.	In 10 hours.	Chill and fever of 40.4° C., with œdema of leg and arm.	Till drug was withdrawn.	Recovery.	Lurmann. Berliner klin. Woch., No. 33, 1876.	Not stated.	Chronic rheumatism.	
Not given. Adult.	F.	30 grs. in one dose.	At once.	A severe chill and a rise of temperature to 40.5° C.; disturbed respiration and heart; sweat, but no rash.	3 days.	Recovery.	Baruch. Berliner klin. Woch., No. 23, 1883.	Not stated.	Polyarthritic rheumatism.	
21	M.	540 grs. were given in all, producing diarrhœa.	After first dose, when drug was renewed.	A diffuse rash, with a chill and a rise of temperature to 40.2° C.		Recovery.	Erb. Berliner klin. Woch., No. 29, 1884.		Articular rheumatism.	On onset of diarrhœa drug stopped for 2 days.
33	M.	120 grs. a day; altogether, 675 grs.	After 5 days.	Gangrene produced by obliteration of femoral artery.	13 days.	Death.	Dujardin-Beaumetz. Bulletin de Thérap., xciii, p. 324.	Not stated.	Articular rheumatism.	Reporter very sure of the result being produced by drug.
Adult.		Not stated.	Not stated.	Vomiting; giddiness; sloughing of axillary glands; rheumatism.	Not stated.	Not stated.	Brit. Med. Journal, p. 2, 1876.	Not stated.	Acute rheumatism.	
30	F.	20 grs. every 2 hours.	After 2 days.	Wildly delirious for entire night.	As long as drug was taken.	Recovery.	Barrows. N. Y. Medical Record, 1882, p. 450, April 29.	Not stated.	Articular rheumatism.	No temperature given.

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 2.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Tempera-ment.	Disease.	Remarks.
Not stated.	F.	In 10 days, took 300 grs.	On 12th day.	Wild delirium, mostly erotic.	3 days.	Recovery.	Bogdanow. London Med. Record, 1882, p. 452; also, Vratsch, 1882, Nos. 12 and 13.	Not given.	Acute rheumatism.	Salicylate of sodium.
44	F.	20 grs. every 2 hours.	On 3d day.	Wild delirium, with much auditory disturbance.	4 days.	Recovery.	Barrows. N. Y. Medical Record, April 29, 1882, p. 450.	Not given.	Articular rheumatism.	No temperature given.
11	M.	10 grs. every 3 hours.	After 6th dose.	Wild delirium, with evil visions.	1 day.	Recovery.	Barrows. N. Y. Medical Record, April 29, 1882, p. 450.	Not given.	Articular rheumatism.	No temperature given.
37	F.	15 grs. every 2 hours.	After 6th day.	Wild delirium.	3 days.	Recovery.	Barrows. N. Y. Medical Record, April 29, 1882, p. 450.	Not given.	Acute articular rheumatism	No temperature given.
35	F.	20 grs. every 2 hours.	Next day.	Wild delirium.	1 day.	Recovery.	Barrows. N. Y. Medical Record, April 29, 1882, p. 450.	Not given.	Acute rheumatism.	No temperature given.
31	F.	20 grs. every 2 hours.	3d day.	Delirium and tinnitus aurium.	6 days.	Recovery.	Barrows. N. Y. Medical Record, April 29, 1882, p. 450.	Not given.	Acute rheumatism.	No temperature given.
50	M.	20 grs. every 2 hours.	3d day.	Actively delirious.	Promptly disappeared.	Recovery.	Barrows. N. Y. Medical Record, April 29, 1882, p. 450.	Not given.	Acute rheumatism.	No temperature given.

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 3.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
28	M.	20 grs. every 2 hours.	After 4 days.	Delirium of a wild type.	4 days.	Recovery.	Barrows. N. Y. Medical Record, p. 450, April 29, 1882.	Not stated.	Acute rheumatism.	No temperature given.
		1 to 1½ drachms.	Immediately.	Delirium of a transient type: headache and dizziness.	Till withdrawal of drug.	Recovery.	Riegel. Berliner klin. Woch., 1876, p. 182.		Rheumatism	
38	F.	15 grs. every hour.	At end of 9th day.	Visual hallucinations.	Till withdrawal of drug.	Recovery.	Schuhmacher. Deutsche Med. Woch., 1876, No. 18.	Hearty and strong.	Rheumatism	
Not stated.	Not stated.	Not stated.	Not stated.	Psychical disturbances, dimness of vision, and flickering before the eyes.	Not stated.	Recovery.	Riess. Berliner klin. Woch., 1877, p. 29.	Not stated.	Diabetes.	
Not stated.	Not stated.	Not stated.	Not stated.	Diminution of acuity of vision and contraction of retinal vessels.	Not stated.	Recovery.	Knapp. Wiener Med. Woch., 1881, p. 1237.	Not stated.	Rheumatism and fever.	
38	M.	½ oz. a day for 9 days.	On 9th day.	Mental depression; severe headache; mental weakness; motor disturbances; ran into objects.	5 days.	Recovery.	Muller. Berliner klin. Woch., 1887, p. 29.	Not stated.	Diabetes.	Salicylate of soda.
		75 grs. at one dose.					Gottdamer. Berliner klin. Woch., 1876, p. 47.	Not stated.	Diabetes.	Quite a number indefinite cases here recorded.
38	M.		At once.	Inflammation of kidneys; hæmaturia and albuminuria; delirium; sweat.	Not stated.	Recovery.	Balz. Arch. für Heilkunde, vol. xviii, p. 65.	Not stated.	Rheumatism	

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 4.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks
		75 grs. a day for 5 days.	5th day.	A petechial exanthem; pruritic petechiæ over the whole body.	8 days.	Recovery.	Frendenberg. Berliner klin. Woch., 1878, p. 630.	Not stated.	Marasmus.	Renewal of drug caused return of symptoms.
Adult.	M.		Immediately.	Pemphigus eruption over the hands and body.	Till drug was withheld.	Recovery.	Rathery. Gazette des Hôpitaux, 1881, p. 149.	Not stated.		
45	M.	1 drachm in one dose.	Immediately.	Redness of left side of face, with intolerable itching; lower extremities and chest also affected; œdema of eyelids, upper lips, and extremities.	24 hours.	Recovery.	Heinlein. Aerztliche Intelligenzblatt, April, 1878.	Not stated.	Articular rheumatism.	
14	F.	150 grs. a day for a week.	Immediately.	Disturbed respiration; œdema of lower limbs and face; albuminuria; diabetic urine; loss of bodily weight.	Till drug was withdrawn.	Recovery.	Caplick. Inaugural Dissertation, Kiel, 1882.	Not stated.	Diabetes.	
						Recovery.	Leonhardi-Aster. Deutsche Zeit. f. pract. Med., 1876, S. 367.			
				Profuse sweats.			Furbringer and Schultze, Arch. f. kl. Med., Bd. xvii, S. 294.			These writers only make general statements.

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 5.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
15	F.	510 grs. in 16 hours.	At once after last dose.	Restlessness; red face; dilated pupils; divergent strabismus; delirium.	7 days.	Recovery.	Petersen. Deutsche Med. Woch., 1877, p. 13.	Not stated.	Surg. disease of foot, with fever.	Drug given hypodermically.
28	F.	825 grs. at one dose, by mistake.	At once.	Dyspnœa; low temperature; rapid pulse.	11 days.	Recovery.	Weckerling. Arch. f. klin. Med., Bd. 19, S. 319.	Not stated.	Pleurisy, fever.	
							Buss. Weber Wesen ü. Behandlung des Fiebers Basel, 1878, S. 174.			
							Cattani. Ann. univers. di med. Triglio, 1879.			
							Jahresbericht f. Pharmakognosie, 1879, S. 259.			
							Jahresbericht f. Pharmakognosie, 1879, S. 259.			
							Kisch. Prager Med. Woch., 1880.			
						Death.	Dixneuf, Etude sur la médication salicylée Thèse. Paris, 1878.			

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
							Empis et Gubler. Bulletin de l'Acad. de Méd., 1877.			
17	F.	510 grs. in 3 doses, 1 each day.	Day after last dose.	Rapid breathing; hebetude; pupils wide open and immobile; "salicylic-acid dyspnœa."	36 hours after last dose.	Death.	Quincke. Berliner klin. Woch., November 20, 1882, No. 47.	Not stated.	Acute rheumatism.	At autopsy, great engorgement of viscera; pericardial ecchymosis and renal hyperæmia.
23	M.	10 grs. every hour for 18 hours.	At 12th hour.	Violent delirium; profuse epistaxis; pulse irregular, and temp. 103° F.; epistaxis repeated.		Recovery.	Cardwell. Therapeutic Gazette, June, 1889.	Not stated.	Articular rheumatism.	
							Woods. Maryland Med. Jour., February 25, 1888.			
							Woods. Maryland Med. Jour., February 25, 1888.			
							Woods. Maryland Med. Jour., February 25, 1888.			
Adult.	M.	192 grs. in one dose by mistake.	"Very shortly."	Nausea and weakness: diarrhœa: vomiting after diarrhœa.	A day or so.	Recovery.	Chisholm. Maryland Med. Jour., January 30, 1886.	Not stated.	Inflammation of eye.	

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 7.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
Middle age.	F.	20 grs. at one dose.	8 hours after dose.	Vision impaired; deafness; excessive headache.	30 hours.	Recovery.	Gibson and Felkier. The Practitioner, January, 1889.	Not stated.	Erysipelas.	
27	F.	20 grs. every 3 hours, then t. d.	On 7th day.	Ringing in ears; epistaxis; hæmorrhage from gums; large clots in mouth.	4 days.	Recovery.	Shaw. Lancet, Jan. 18, 1889.	Not stated.	Acute rheumatism.	
18	F.	10 grs. t. d.	After 3 days.	Sudden rise of temperature; nausea and vomiting; appeared to be dying.	Several days, till drug was stopped.	Recovery.	Dreschfeld. Medical Chronicle, 1884–85, p. 238.	Not stated, but anæmic and weak.	Nephritis.	
Adult.	M.	15 grs. t. d.	In a few days.	Urticaria of a severe form.	Not stated.	Recovery.	Dreschfeld. Medical Chronicle, 1884–85, p. 242.	Not stated.	Articular rheumatism.	
Adult.	F.	A vaginal wash of drug.	At once.	An eruption like erythema nodosum.	More than 4 days.	Recovery.	Dreschfeld. Medical Chronicle, 1884–85, p. 242.	Not stated.	Vaginal disorder.	Used a vaginal wash.
				Great dyspnœa and death.		Death.	Ogston. British Med. Journal, 1883, vol. i, p. 869.			
Not stated.		Not stated.	Sudden.	Great dyspnœa and death.	Short.	Death (?)	Dreschfeld. Medical Chronicle, 1884–85, p. 243.	Not stated.	Phthisis.	
34	M.	20 grs. 3 times a day.	On 3d day.	Great dyspnœa and cyanosis; nausea and headache.	24 hours.	Recovery.	Dreschfeld. Medical Chronicle, 1884–85, p. 243.	Not stated.	Articular rheumatism.	

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 8.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Tempera-ment.	Disease.	Remarks.
15	F.	401 grs. in 12 hours.	After last dose.	Symptoms were exceedingly severe; skin reddened; ringing in ears.	Short.	Recovery.	Nathan. Inaug. Dissertation, Kiel, 1875.	Not stated.	Rheumatism	
Adult.	F.	Not stated.	After last dose.	Mental delusions of of a depressant character; much weeping; lucid intervals.	About 8 days.	Recovery.	Binz. Berliner klin. Woch., No. 27, 1876.	Not stated.	Rheumatism	
Adult.	F.	340 grs. in 12 hours.	After last dose.	Mental delusions; not much melancholia, and was quite cheerful.	A few days.	Recovery.	Stricker. Berliner klin. Woch., No. 8, 1876.	Not stated.	Rheumatism	
50	F.	380 grs. in 3 days.		Delirium; absurd delusions; insomnia; urine dark and albuminous.	24 hours.	Recovery.	Daly. Brit. Med. Journal, January 19, 1878.	Not stated.	Rheumatic fever.	
26	M.	20 grs. every 4 hours.	2 days.	Spongy gums, bleeding on touch; cyanosis; profuse sweat.	1 week.	Recovery.	Shaw. Lancet, Jan. 18, 1889.	Not stated.	Acute rheumatism.	
15	M.	20 grs. every 3 hours.	Many days after first dose.	Epistaxis; heart's action wild and tumultuous; retinal hæmorrhages.	Eye permanently blind.	Recovery, all except the eye.	Shaw. Guy's Hosp. Reports, 1886–87.	Not stated.	Acute rheumatism.	
21	F.	20 grs. every 2 hours.	After 6 doses.	Hæmaturia; ecchymosis of kidneys and bladder.	1 day.	Death.	Shaw. Guy's Hosp. Reports, 1886–87.	Not stated.	Acute rheumatism.	Salicylate of sodium.
26	F.	22 grs. every 3 hours.		Delirium; ecchymosis of kidneys; hæmaturia.	3d day.	Death.	Shaw. Guy's Hosp. Reports, 1886–87.	Not stated.	Typhoid fever.	

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 9.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
Not stated.	F.	"Medicinal doses."	Not stated.	Purpura and hæmaturia.	Not stated.	Recovery.	Millican. Reported to Med. Soc. of London, 1882.	Not stated.	Acute rheumatism.	Had had hæmoptysis as vicarious mens. before.
25	M.	20 grs. every 2 hours.	Next day after first dose.	Repeated epistaxis, with weak heart.	For several days.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicin used.
30	M.	20 grs. every 2 hours.	8th day after first dose.	Vomiting and headache.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicin used.
7	M.	10 grs. every 2 hours.	After 10th dose.	Great fall of temperature to 96° F.	A few hours.	Recovery.	Seen by myself in wards of hospital.	Nervous.	Acute rheumatism.	Salicin used.
24	M.	20 grs. every 2 hours.	On 2d day.	Weak pulse, with epistaxis.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicin used.
28	F.	20 grs. every 2 hours.	On 2d day.	Profuse nose-bleed; delirium; heart-failure.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
28	M.	15 grs. every 2 hours.	On 3d day after first dose.	Miliary rash on body; sudamina; delirium; giddiness.	Some days.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
40	M.	15 grs. every 2 hours.	2d day after first dose.	Deafness and epistaxis.	Some days.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 10.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
18	F.	15 grs. every 2 hours.	After a few doses; 2d day.	Epistaxis, deafness, and delirium.	Till drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
16	F.	15 grs. every 2 hours.	Soon after first dose.	Sick stomach; deafness; delirium; vomiting.	As long as drug was used.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
5	F.	Not stated.	At once.	Bad sick stomach.	As long as drug was used.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
16	F.	15 grs. every 2 hours.	Next day.	Sick stomach and hæmatemesis.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
30	M.	15 grs. every 4 hours.	10 days after first dose.	Sore throat; vomiting; deafness.	As long as drug was used.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
17	F.	15 grs. every 2 hours.	On 5th day.	Intense headache; weak heart.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
14	M.	15 grs. every 2 hours.	Next day.	Vomiting; deafness; feeble pulse.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
24	M.	15 grs. every 4 hours.	Next day.	Deafness; vertigo; wandering of mind and epistaxis.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 11.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
20	F.	30 grs. every 2 hours.	Soon after beginning drug.	Vomiting; deafness; transient albuminuria.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
19	M.	15 grs. every 3 hours.	On 5th day.	Deafness and severe headache.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
14	M.	10 grs. every 4 hours.	On 2d day.	Delirium; deafness; vertigo; heart feeble.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
45	M.	15 grs. every 3 hours.	On 2d day.	Deafness; wandering; bad frontal headache, and noise in ears; delirium.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
19	M.	15 grs. in 1 dose.	At once.	Depression; deafness; vomiting.	Short.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
19	M.	15 grs. every 3 hours.	At once.	Heart feeble; delirium; epistaxis; vomiting.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
19	M.	15 grs. every 2 hours.	At once.	Deafness, epistaxis, and cardiac depression.	A few hours.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
13	M.	15 grs. every 3 hours.	Next day.	Deafness; delirium; persistent vomiting.	Until drug was stopped.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.

UNTOWARD EFFECTS OF SALICYLIC ACID, No. 12.

Age.	Sex.	Dose.	Time of Onset.	Symptoms.	Duration.	Result.	By whom and where Reported.	Temperament.	Disease.	Remarks.
24	F.	30 grs. every 2 hours.	On 2d day.	Delirium; epistaxis; headache; vomiting.	As long as drug was used.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
46	M.	15 grs. every 4 hours.	On 2d day.	Deafness, vertigo, and tinnitus aurium; vomiting.	As long as drug was used.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
21	M.	15 grs. every 2 hours.	1 day.	Headache; vertigo; deafness; diarrhœa.	As long as used.	Recovery.	Greenhow. Clinical Soc. Trans., London, 1880.	Not stated.	Acute rheumatism.	Salicylate of sodium.
Adult.	M.	75 grs. in one dose.	At once.	Vomiting; diarrhœa; profound collapse and hæmorrhage from the nose.	A few hours.	Recovery.	Pullmann. Berliner klin. Woch., July 1, 1889.	Not stated.	Orchitis, as a sequela of mumps.	Salicylate of sodium.
22	M.	Ordinary doses.	After a few doses.	Intestinal hæmorrhage.	As long as drug was used.	Recovery.	Pullmann. Berliner klin. Woch., July 1, 1889.	Not stated.	Acute articular rheumatism.	Salicylate of sodium.

On looking over these tables we find that the following facts may be gleaned from them.

In the first place it is evident that age has some predisposing effect, as may be seen from the following table:—

Males.		*Females.*	
1 to 10 years,	1 case.	1 to 10 years,	1 case.
10 to 20 "	11 cases.	10 to 20 "	8 cases.
20 to 30 "	10 cases.	20 to 30 "	7 cases.
30 to 40 "	5 cases.	30 to 40 "	5 cases.
40 to 50 "	4 cases.	40 to 50 "	2 cases.
50 to 60 "	— cases.	50 to 60 "	— cases.
60 to 70 "	— cases.	60 to 70 "	— cases.
Adults, no age stated, . .	3 cases.	Adults, no age stated, . .	5 cases.
	34 cases.		28 cases.

It will be seen that the ages most commonly exhibiting untoward effects are from 10 to 40 years in both sexes, which is rather remarkable, since the old are so frequently rheumatic that one would expect to find cases between 50 and 70 years.

That sex exercises little effect is seen very well in the columns just given, although the males seem to suffer a little more frequently than the females, probably because males more frequently have rheumatism, owing to exposure.

The size of the dose producing evil effects varied very greatly; sometimes it amounted to saturation of the system by prolonged administration of large amounts. In others it followed after as little as 60 grains in one dose. Mild untoward effects, of course, followed smaller amounts.

The time of onset naturally varied with the mode of ingestion of the drug, and two classes may, therefore,

be formed, those in which bad effects occurred after a single dose and those in which the effects came on after many large doses. In most of the former the symptoms came on at once, while in the second series of cases the time varied too much to make it possible to draw conclusions.

The symptoms most commonly seen were collapse, profuse cold sweats, giddiness, headache, and delirium, especially at night. This last symptom, with headache, was more common than all the rest.

No exact time of duration can be determined upon. In some cases the symptoms passed away at once on the withdrawal of the drug, in others they continued for days, or, in those cases where the lesions were serious, went on to death or a life of invalidism or chronic disease, as in cases of retinal hæmorrhages.

The results, so far as recovery or death is concerned, are encouraging,—only 7 deaths in 59 cases. It is to be noted, however, that, unlike the deaths from the other antipyretics, where a serious disease, sufficiently severe to be capable of destroying life was present, in these cases the drug seems to have been largely, if not entirely, responsible for the fatal effect. On the other hand, it must be remembered that, as a rule, the doses given to these cases were very large, and the drug continued after signals of distress had been displayed to a sufficient degree to make it proper to discontinue the medicament at once.

The temperament and occupation of the cases recorded are not eligible for study, owing to faulty reports.

The diseases in which untoward effects manifested themselves were as follow :—

Acute articular rheumatism,	48	Ophthalmia,	1
"Rheumatism,"	7	Erysipelas,	1
Diabetes,	4	Nephritis,	1
Fever,	2	Vaginal discharge,	1
Chronic rheumatism,	1	Phthisis,	1
Marasmus,	1	Typhoid fever,	1
Pleurisy,	1		

Acute rheumatic cases are the most frequent chiefly because of the common employment of the drug in this disease, although it would seem probable that the alterations in the blood produced by the rheumatic poison may have had some effect, combined with the action of the drug.

A very interesting review of a number of these cases has been contributed by Shaw, in Guy's Hospital Reports for 1886–87, the patients having been inmates of this institution.

The following table gives the statistics of the cases for 1881 and 1886 :—

	1886.	1881.
No toxic effects mentioned,	23	40
Toxic effects,	49	62
Delirium,	12	21
Deafness,	28	33
Vomiting,	17	15
Tinnitus,	13	16
Headache,	21	12
Epistaxis,	5	6
Irregular or slow pulse,	9	4
Albuminuria,	2	4
Hæmaturia,	1	1
Retinal hæmorrhage,	—	1
Urticaria,	—	1

There is one point to be remembered in relation to these cases of untoward symptoms. In a very large number of them the drug used was out of all proportion to the effect desired, and in some cases the dose

was pushed beyond the boundary of the medicinal into that of the poisonous.

The clinical evidence of the value of salicylic acid may be divided into three parts, namely, as an antipyretic, as an antiseptic, and as an antirheumatic. The first of these divisions naturally, in this instance, attracts us the most.

The employment of salicylic acid as an antipyretic was resorted to by Butt,[1] in 1875, and immediately afterward a very large number of other clinicians hastened to record their observations upon it, among the first of whom may be mentioned Furbringer,[2] Senator,[3] Jahn,[4] Nathan,[5] Riess,[6] Gottdammer,[7] Bertholet,[8] Weber,[9] Steinitz,[10] and Buss,[11] as well as Hiller,[12] Pel,[13] Wagner,[14] Buch,[15] Schultz,[16] Molli,[17] Fischer,[18] and Wolfberg.[19] This list of names by no means completes the bibliography of the short space of less than one year, but gives a fair idea of the immense number of papers given us immediately on the introduction of the acid as an antipyretic.

[1] Centralblatt für die Medicin. Wissenschaft., No. 18, 1875.
[2] *Ibid.*
[3] Berliner Medicin. Gesselschaft, June 2, 1875.
[4] Der Feldartz, No. 1, 1876.
[5] Deutsche Zeitschrift für Prakt. Med., No. 2, 1876.
[6] Berliner klin. Wochenschrift, Nos. 50 and 51, 1875.
[7] *Ibid.*, No. 4, 1876.
[8] Archiv für Heilkunde, 2 und 3 Heft, 1876.
[9] Allgemeine Med. Central. Zeitung, March 25-29, 1876.
[10] *Ibid.*, Feb. 13, 1876.
[11] Deutsche Archiv für klin. Med., Bd. xv, Heft 5 and 6.
[12] *Ibid.*, xvi, 1875.
[13] *Ibid.*, Bd. xvii, 1876.
[14] Journal für Prakt. Chemie, Bd. ii, 1875.
[15] Allgemeine Med. Central. Zeitung, February 26, 1876.
[16] *Ibid.* February 16, 1876.
[17] Berliner klin. Wochenschrift, No. 38, 1875.
[18] Deutsche Zeitschrift für Prakt. Med., No. 13, 1875.
[19] Deutsche Arch. f. klin. Med., Bd. xvi.

Perhaps no better way of studying the subject can be found than to speak of the results of these clinicians collectively, reserving special mention for those whose papers deserve much recognition.

Every observer who has used salicylic acid must have noted a fall of temperature of a more or less marked form, and they have also noted that if the drug be at all cumulative in its action this fall may go on into a subnormal temperature, and even to collapse. Further than this, all clinicians are in accord with a statement made by the writer elsewhere, viz., that the antipyretic power of the drug depends very largely upon the disease, the dose, and the severity of the fever.

Typhoid and Other Low Fevers.—In such fevers as these there can be no doubt but that salicylic acid no longer occupies a position of much importance, and, indeed, it may be said that its use is hardly to be thought of unless under most unusual circumstances. The reasons for this are several, but chief among them is the relaxation and collapse which we clinically observe after the use of the drug, and the fact that we have far more sure, active, and agreeable measures, equally convenient for use. Further than this, the writer has found that salicylic acid either does not lower fever at all, or, if it does do so, acts very suddenly and with unlooked-for and undesirable power. Again, the general experience is that the acid often sweats the patient profusely without lowering the fever, whereas, with the other antipyretics, the sweat comes with the fall. All the evidence that we have shows that the course of typhoid fever is in no way shortened by the drug. These are the facts most generally received, but it is but fair to state that other opinions, even of a very

recent date, are held by well-known men. Huchard[1] uses the salicylate of magnesium with great success in typhoid fever, and asserts that 45 to 90 grains in each twenty-four hours relieves the ataxic symptoms and changes the asthenia into greater strength. Jackson[2] and King[3] also speak well of the acid under such circumstances, and Sullivan[4] regards it as very efficacious.

In the fever of phthisis the drug has nothing to recommend it, and much to condemn its employment, as, for example, the profuse sweats, which become worse under its influence. The tendency to gastric disorder, always present in tuberculosis, is decidedly increased by its use.

Sthenic Fevers.—The contra-indications to the use of salicylic acid in these affections are not so pressing as in the fevers of an asthenic type, while the sweating is often excessive and even weakening in its results. The chief objection is the irritation of the gastric mucous membrane, and the fact that we have so many better remedies of the same class.

Upon malarial fevers the drug seems to have a slight antiperiodic influence.

Rheumatism.—The employment of salicylates in rheumatism is both for their specific influence and their antipyretic power, yet there are some in the profession who, even at the present day, would have us believe that such a specific action does not exist. There are others, too, who assert that the severity of the disease, so far as continuances or relapses are concerned, is not favorably affected by the drug. Thus, Hood[5] has col-

[1] Journal de Méd. de Paris, January 15, 1888.
[2] Medical Standard, March, 1888.
[3] Weekly Medical Review, June 30, 1888.
[4] Medical Standard, March, 1888.
[5] London Lancet, February, 1888.

lected the records of over 2000 cases of acute sthenic rheumatism of a typical character, more than one-half of which were treated by salicylates, and in the analysis made by him it appears that while the drug caused a decrease in pain and a fall of temperature, its use was also followed by more relapses than occur under the older methods of treatment, and it left the patients much enfeebled. It had no effect whatever over the cardiac lesions, and the mortality was in no way decreased.

COLD BATHING.

From the title prescribed by the Boylston Prize Committee it is not to be supposed that the employment of the cold pack or bathing is to be considered in the treatment of fever in this essay, yet one can scarcely pass by this important subject without calling attention to its usefulness.

Used, as was cold bathing, many years before the use of antipyretic remedies in fevers, it was at one time in great danger of being lost sight of in the struggle for internal febrifuges; yet, no one having large experience in hospital or private practice can think but that such methods are equal to or more useful than the drugs. Cold bathing is a power for good before which every other measure must stand aside.

While such a conclusion is generally accepted to-day by almost every one, we have in reality passed through a period in which the opinions of many men were greatly disturbed and opposed to one another, and von Ziemssen has recently put the opinions of all these opposing factions in so concise a form that it may be permissible to quote him in this place. Speaking of the worth of antipyresis in any form, he divides the writers of the last twenty years into groups as follows :—

The extreme hydriaticists, who use only the cold bath, and reject internal antipyretics, such as Brandt, Vogel, Winternitz, and others.

The moderate hydriaticists, who resort to lukewarm baths, but reject internal antipyretics, among whom may be named Naunyn and others.

Those who, according to indication, resort to moderate hydrotherapy and to internal antipyretics, such as Liebermeister, Jurgensen, and Riess.

Those who consider fever as a salutary and necessary regulator, and only resort to antipyretics when dangerous symptoms arise, as Heubner, Curschmann, and others.

Those who claim that fever is a necessary phenomenon, and, therefore, reject all attention to antipyresis and attend to diet (Glaser).

Those who absolutely deny the influence of treatment on the mortality of fever (Port).

Truly, it would be hard to find a set of more diverse and contradictory opinions in regard to so limited a subject; but, fortunately, the practice of Liebermeister, Jurgensen, and Riess has virtually proved the value of cold, and it is resorted to by most of us. Those who have tried it rely on this method very extensively.

A very important question arises as to the value of the cold pack in private practice. There can be no doubt of its acting very well if carefully carried out under such circumstances. It is certainly much the best remedy where trained nurses are at hand to administer it, but where only members of the family are to care for the sick man, and the doctor can only be on hand once in twenty-four hours, it is manifestly impossible to use it. Even if the bath be properly given, the exhaustion produced by clumsy handling may overbalance all the good to be achieved.

It has been claimed that the cold pack never results in cardiac failure, as does the use of antipyretics. The author is quite confident of the fallacy of this statement; indeed, he has but recently seen such a case. The cold pack cannot be used any more blindly than the antipyretic drug, and it is probable that when this measure is more widely employed more reports of untoward effects will appear in the medical magazines.

CONCLUSIONS.

An essay having a large and extensive bibliography is almost useless unless the writer finally gives the results reached from his studies in so short, concise, and distinct a form as to enable the reader to carry away with him a clear conception of the ideas which the mass of material should be productive of in his thought and practice.

From the reading of a large amount of literature on this subject, the writer thinks it may be stated that antipyrin stands to-day foremost in the ranks of the antipyretics, with antifebrin next, while thallin and phenacetine follow, with perhaps a preference for the latter. These conclusions are in regard to the reduction of fever. In pain the arrangement should be somewhat changed. Antipyrin still takes the lead, but phenacetine is quite as useful an analgesic as antifebrin, and seems more safe. Thallin possesses hardly any such power.

In rheumatism, of course, the salicylates act better than the rest of the class of antipyretics, particularly in reference to the pain and the cure of the disease itself, but the others control the fever of rheumatism in a much more effective manner.

As a general rule, marked depression and adynamia contra-indicate the use of all antipyretic drugs, although exceptions to this rule, of course, occur.

For wide-spread application, to be put in the hands of the inexperienced, to be efficacious and yet quite harmless, cold sponging is the antipyretic remedy *par excellence;* but even this must be used carefully and with intelligent ideas of its objects and results. The

greatest enemies of antipyretic treatment are its friends, who, in their enthusiasm, often fail to use discretion and employ the measures to excess, or without regard to the indications really at hand.

There can be no doubt but that antipyresis is an addition to our remedial measures of vast value, and the suffering which it relieves is one of the blessings which follow increased knowledge and the new era of therapeutical training.

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