

*"Pyrexia
and its Treatment by
Antipyretics"*

Thesis for the Degree of M.D.

By

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"Pyrexia and its Treatment by Antipyretics"

As the title of this paper will show its object is to deal with that increase of temperature which occurs in the human body during the course of many different diseases.

It does not profess to enter into the causes of pyrexia. This is a subject which is surrounded with difficulties, and with regard to which there is great difference of opinion.

One thing, however, may be stated as an acknowledged fact, that in pyrexia, no matter from what cause, there is some disturbance of the normal relation which exists between heat production and heat loss. In other words, the regulation of the thermogenic and thermolytic processes is thrown out of gear.

It may not be out of place here to mention a few facts with reference to the regulation of the temperature during health and the

means by which this is accomplished.

Broadly speaking, the bodily temperature of a man during health is uniform, without regard to the temperature of the climate in which he lives; and no matter whether his occupation exposes him to extreme heat or extreme cold.

No doubt there are slight variations during the course of each day, the temperature oscillating above and below 98°F .; but these are so slight and unimportant, that in making a broad general statement we may say, that the temperature of the human body during health is a fixed quantity (98°F), and is the same in persons living in all parts of the globe.

This uniformity of temperature implies that there is a mechanism within the body itself, which regulates and governs the relation between heat production and heat loss.

The greater part of the heat of the body is the result of chemical changes occurring within. In fact if we exclude what may

(11) Practitioner Hand-book of Treatment
Fothergill. Third Edition page 78

possibly be gained by the ingestion of hot food, and what may possibly be gained by the friction caused by mechanical movement, we may say that all the heat of the body is due to chemical reactions.

(1) Formerly it was supposed that heat was produced only in the lungs. That they were as Fothergill terms them "the furnaces of the body". Now we know that heat is produced in all parts of the body. Heat is evolved whenever oxidation is going on. In the lungs oxygen passes from the air to the blood oxidising the latter, and no doubt a considerable amount of heat is evolved during the process. But in the capillaries, in all the tissues of the body, oxygen passes from the blood to the tissues, and here also a process similar to combustion is going on heat must be evolved.

Heat is lost partly by conduction and radiation but chiefly by evaporation, and this to some extent from the lungs but

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chiefly from the skin. Generally when there is a copious supply of blood to the skin the sudoriferous glands are stimulated to action and profuse perspiration is the result. This is almost always the case, but some times; as for example in some stages of fever, we may have increased vascularity of the skin without perspiration. And on the other hand, in some cases, as in syncope, we may have profuse perspiration while there is great pallor and apparent anaemia of the skin.

These, however, are exceptional cases. It may be stated as a rule that when there is increased vascularity of the skin there is perspiration. Now the point which seems to me to be important from a practical point of view is, that it is not the production of sweating that reduces the temperature but the evaporation of the sweat. It is a fact, well known in physics, that a certain amount of heat becomes latent when a

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solid is converted into a liquid or when a liquid is converted into the gaseous form. And, to me, it seems that it is the conversion of the sweat into the gaseous form, rendering a certain amount of heat latent, which to a great extent reduces the bodily temperature.

During health there is a relation between the amount of heat produced in the body and that which is lost from it. When the temperature of surrounding objects is low; that is, when the amount of heat lost from the body by the skin would be considerably in excess of the heat produced; the capillaries in the skin contract. This has the effect of reducing the volume of blood which comes to the surface of the body, and consequently lessens the loss of heat from the skin. At the same time more blood is sent to the internal organs on the action of which the production of heat so largely depends. In short under

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The circumstances above mentioned we have an increase in the amount of heat produced and a diminution in the amount lost, the result being that the temperature of the body is not lowered to any extent by the surrounding temperature.

On the other hand when the surrounding temperature is very high the superficial vessels dilate and more blood reaches the surface of the body. The result of this is that the loss of heat from the skin is increased, while at the same time, less blood reaches the internal organs and consequently the heat production is diminished.

This contraction and dilatation of the superficial blood vessels is a reflex phenomenon and is controlled by the Vaso-motor nerves and the Vaso-motor center in the Medulla Oblongata.

There are other causes (although of much less importance) which assist in the maintenance of an equable temperature. The most important

of these are food and clothing.

In Cold climates the people instinctively consume large quantities of fat in their food, and wear clothing made of such material as shall reduce the loss of heat from the skin to a minimum.

In warmer climates the food is more varied in character and the clothing is not of such non-conductable material.

Then again in very warm climates the food is chiefly of such a nature as has very little heat producing properties, and the clothing is such as to permit as far as possible free loss of heat from the skin.

Having thus far considered the temperature of the human body in health I now pass to what is more particularly the subject of this paper, namely, abnormal increase of the temperature.

Many diseases with which the physician is called upon to deal are associated with an increased bodily temperature. Considering the

(11) Principles & practice of Medicine. Jaffe & Pyle-Smith
Third Edition. Vol I. page 32.

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matter theoretically there are three different conditions which may give rise to an increased temperature.

1. Diminished heat loss.

(1) This is a possible cause of pyrexia although it is not now considered to be of much practical importance. In 1863 the late prof Franke propounded the theory "that the amount of heat generated during fever is the same as in health, so that pyrexia would consist in a diminution in the amount of heat given off from the body"

2. Increased heat production.

It is now an established fact that in pyrexia there is an increased amount of chemical change going on in the tissues of the body. We have evidence of this in the increased amount of urea excreted. If then there be increased oxidation of the tissues of the body, as a result we shall have increased production of heat.

3. A Combination of both of the above conditions.

As stated above there is no doubt that in febrile diseases there is an increased amount of chemical change going on in the body, as evidenced by the increased amount of urea excreted in the urine. But if, in addition, we have (as sometimes happens in the early stage of acute pyrexia) a dry skin and to some extent contraction of the superficial blood vessels, the diminution in the amount of heat lost from the skin will be sufficient to considerably influence the rise in temperature.

In all cases of pyrexia, however, one thing is clear, that the balance which exists in health between heat production and heat loss has been disturbed.

The cause of the increased tissue change in febrile disorders is a question with which I do not propose to deal. It is one with regard to which there is great difference of opinion and one which is surrounded with difficulties.

(11) Harvest 21st July 1888 page 120

But a question of some importance and one with regard to which there is also some difference of opinion is, is this increase of temperature dangerous to life? Apart from the cause of the fever does the elevated temperature constitute a danger to the life of the patient? This is a most important question. The whole plan of treatment depends on our answer. If pyrexia "seu re" be a danger to life, then when the temperature rises beyond a certain limit it demands our attention. But if, on the other hand, as Cohnheim and some others believe "that fever is not wholly or in itself injurious, but that it may act by destroying the virus, or at anyrate by hampering the conditions essential to the development and spread of the specific microphyte so as to be in itself an expression of the "vis medicatrix naturae". If this be the case we may not only neglect it altogether, but may look upon it rather as a most favourable symptom. This is a theory with

(1)

- (1) Lancet 7th July 1888 page 6.
- (2) Medical Thermometry. Wunderlich page 7
New Sydenham Society. 1891.
- (3) Practitioner Handbook of Treatment
Fothergill page 85.

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which most authorities do not agree. I quote the following in support of the opposite view.

- (1) Hiebermeister says "a patient whose temperature keeps persistently at 104° or higher will certainly die from this cause alone, either after a few days, or after a somewhat longer interval according as his power of resistance is less or greater."
- (2) Wunderlich in classifying temperatures says "Temperatures of $107.6^{\circ}F$ or more are temperatures which in every known disease, except relapsing fever, in all probability indicate a fatal termination."
- (3) Wunderlich also says "a pyretic condition may extend from a mere condition of feverishness, with a temperature of from $99.5^{\circ}F$ to 101.5° states often found in children without any sinister meaning whatever; up to a high febrile state of from 107° to 108.5 beyond which existence is possible for only a brief period, and recovery impossible." And Fothergill remarking on this statement says "Though there are some isolated cases to the

- (1) Furleyson's Clinical Manual. Second Edition page 79
- (2) Theory and practice of Medicine Bristow
Fifth Edition page 107.
- (3) Theory & Practice of Medicine. Bristow. page 110

contrary this statement of Wunderlich is almost universally true."

- (1) Finlayson says "Very high or very low temperatures may also, as a rule, be regarded as evidencing in themselves, a dangerous condition."
- (2) Bristow says "If the temperature exceed 105° the febrile disturbance is excessive, and there is usually considerable danger; from 106° upwards the temperature is frequently termed hyperpyretic; and (with one or two notable exceptions) if it surpass 107° or 108° death is almost certain to supervene."
- (3) Bristow also says "Nevertheless it is obvious, if we consider the physiological and other recognized consequences of fever, that fever itself tends to the induction of death in some two or three different ways. The chief of these appear to be asthenia, blood poisoning and the direct influence of sustained high temperature."

These are opinions which my own limited

experience confirms. In the nine months during which I had the privilege of being an Assistant physician in the City of Glasgow Fever Hospital at Belvidere, I am not aware of a single case of recovery from any infectious disease where the temperature had exceeded 107° F.

Treatment by Antipyretics

What we want to do is to reduce the temperature. The most rational and sure method of doing so, is to remove the cause and within the last few years much has been done in this direction. A number of febrile diseases have been found to be caused by specific Micro-organisms, and for some of these diseases, substances have been prepared which are intended to destroy the micro-organisms and hence remove the cause of the pyrexia. We have examples of this in Sir Joseph Lister's antiseptic method of treating wounds; in Pasteur's treatment of Hydrophobia; and in the treatment of Diphtheria by

antitoxine serum. Probably as the science of Bacteriology advances there may be found similar methods of treating other diseases with equal success.

The term Antipyretics, in its broadest sense, may be used to include not only the drugs which go by that name, but also all physical or mechanical means of getting rid of heat.

It seems to me that for practical purposes antipyretics may be divided into two great classes.

- I. Those which reduce the temperature mainly by the direct abstraction of heat from the body.
- II. Those which reduce the temperature mainly by promoting perspiration.

In considering the subject broadly I consider that Antipyretic methods of treatment differ sufficiently in their mode of action to deserve this classification.

In the first class we include the application of cold in its many different forms.

1. Cold Sponging.

Sponging with water at the ordinary atmospheric temperature (60° to 90° F) is a method which is perfectly safe, if carried out without any unnecessary exposure of the patient. The best method is to sponge the patient under the bed clothes doing one part at a time and having it dried before passing on to another part.

This is a method which reduces the temperature chiefly, if not altogether, by the direct abstraction of heat from the skin. No doubt also if there be much friction used during the process of drying, the amount of blood in the superficial vessels may be increased, and in this way may increase the amount of heat lost from the skin.

I have used cold sponging in a number of moderate cases where I considered no very active measures were called for; and my opinion is, that as an antipyretic, this method is not by any means powerful and its effect is very transient. However, apart altogether

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from its antipyretic action, my experience has been that it is particularly comforting to patients suffering from pyrexia.

2. Iced drinks and Ice to Suck.

This may seem a very trivial method of applying cold and as an antipyretic an unimportant one; but there is no doubt it has some influence in reducing the temperature.

But even apart from its antipyretic action, like cold sponging, it is very refreshing to the patient who is suffering from acute pyrexia.

3. The Cold Pack.

There is no doubt that the cold pack does reduce the temperature very rapidly, and in suitable cases it seems to be very beneficial; but, to my mind, there are serious objections to its use. The tendency to collapse during the pack must always be kept in mind. Indeed, in some cases, this is so great as to prohibit the

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use of the cold pack altogether.

In the cases which I have had the privilege of observing, the immediate effects of the cold pack were very satisfactory. There was a marked diminution in the rapidity of the pulse, a very decided fall in the temperature, and marked quieting of the nervous symptoms. But in most of the cases the effect was transient, indeed in some of them the temperature was as high as ever again in about three hours.

The cold pack was used as follows.

A bed was placed alongside the patient's bed, and on it were spread a waterproof sheet and a blanket. A sheet was wrung out of water which had been standing in a basin for a short time, so as to be about the temperature of the atmosphere; and this sheet was spread over the blanket. The patient, after being stripped of all his clothing, was then laid on the sheet and the ends were folded over him so as to cover his whole body with the exception of the

head and neck. He was then covered up with the blanket. After one hour he was put back into his own bed, dried under the bed-clothes, and, if necessary, a hot bottle was put to his feet.

The following are the details of a case.

J. J. aged 7 years, a strong and well nourished girl, was admitted into the City of Glasgow Fever Hospital at Belvidere on the 5th April 1891 suffering from Scarlet Fever. The history given was, that the illness commenced the previous day with sickness, headache, sore throat, and vomiting: rash was first seen on the day of admission. The symptoms were well marked and there was a good rash.

Everything was going well until the end of the first week. Then the throat became worse and the temperature began to rise considerably.

On the evening of the 12th April (i.e., on the eighth day of the illness) the following note was made. Temperature 104.2°, patient Very

restless; rapid full pulse high tension; throat much inflamed, both tonsils swollen and the right one ulcerated; slight enlargement and tenderness of the lymphatic glands at the angle of the jaw.

After a consultation it was decided to use the cold pack. The patient was cold packed three times; each pack lasting for one hour, and below is a note of the temperatures

1891

12 th	April	8 P.M.	Temperature	104° 2.	Cold pack.
"	"	9-20 "	"	101.6	
"	"	10-20 "	"	103.2.	
"	"	11. 20 "	"	106.4	Cold pack.
13 th	"	12.45 am.	"	101.6	
"	"	1.45 "	"	100.8	
"	"	2.45 "	"	104°	
"	"	3.45 "	"	106.8	Cold pack.
"	"	5 "	"	102.6	
"	"	6 "	"	103.4	
"	"	7 "	"	105.2	
"	"	8 "	"	106.8	

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In this case it was considered injudicious to continue the use of the cold pack; and the temperature continued to rise until just before death it reached 106.8.

Here are the details of another case.

B. C. a little girl, aged 2 years, was admitted into Bellevue Hospital suffering from Scarlet Fever. On admission there was a rash which, though not profuse, was quite characteristic. The throat was congested and the lymphatic glands at the angle of the jaw could be felt distinctly. The urine was free from albumen.

On the fourth day the patient became very restless and a slight convulsion was observed; temperature 105.4.

It was considered advisable to use the cold pack. In this case also three packs were given each one lasting for an hour.

On the next page are the temperatures taken every hour, in the rectum.

10 a.m.	Temperature	105.4	Cold pack
11 " "	"	104.8	
12 noon	"	105.	Cold pack
1 P.M.	"	102.4	
2 " "	"	104.	
3 " "	"	106.6	Cold pack
4 " "	"	103.4	
5 " "	"	104.4	
6 " "	"	104.	
7 " "	"	103.8	

After this the temperature never rose above 103°. The nervous phenomena gradually disappeared and the case went on well towards recovery.

I have observed other two cases of Scarlet Fever in which the cold pack was used. I am sorry the details have not been kept. The one case was cold packed once, the other twice but both patients died with hyperpyrexia. All four cases have this in common;

that while the cold pack caused an undoubted reduction in the temperature, after a few hours the temperature was almost as high as it was before the pack was used.

4. The Cold, or Gradually Cooled, Bath.

This is a method of reducing the temperature of which I have no personal experience.

The bath has perhaps been employed more particularly in typhoid fever than in any other febrile disease. It would, however, probably be useful in pyrexia from any other cause provided there were no renal, cardiac, or pulmonary complications to contra-indicate its use.

In most patients the shock of the cold bath must be great. However in some cases it may be beneficial, but in many cases it might be fraught with great danger. In my mind it would seem better in most cases to use the tepid bath, and have it gradually cooled while the patient is in it,

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either by the addition of cold water or ice.

We pass now to the second class of Antipyretics.

II. Those which reduce the temperature mainly by promoting perspiration.

1. Tepid Sponging.

Sponging either with tepid water alone, or with tepid water and acetic acid, is a good method and seems to be very comforting to the patient. I have used this method with good results in cases where the temperature was not so high as to demand more heroic treatment.

This method probably does not differ materially from cold sponging. However with tepid water there can be very little, if any, direct abstraction of heat from the skin. The chief difference seems to me to be that tepid water causes more rapid determination of blood to the skin, and in this way, promotes perspiration more quickly, while, at the same time, the acetic

acid assists evaporation.

2. Hot Pack

This is a method which was sometimes employed at Bellevue; where either with or without sponging, the patient is rolled up in blankets and surrounded by hot bottles. This is a method of producing perspiration. Once perspiration has been established I think there should not be too large a supply of blankets. This is clear when we remember that it is not only the perspiration which reduces the temperature but the evaporation of the sweat. If the patient be thickly covered with blankets, and especially if he be rolled up in one, he may be bathed in perspiration but it cannot evaporate to any extent.

This method is, no doubt, very good in cases of kidney affection where we want to secure the compensatory action of the skin. But if we adopt the hot dry pack as a means of reducing

the temperature it is necessary to promote the evaporation of the perspiration so produced.

3. Drugs which reduce the temperature.

Drugs which reduce the temperature are very numerous and very little is known about many of them. They may be divided into three classes.

- A. Diaphoretics
- B. Specific Antipyretics
- C. Antipyretics.

A. Diaphoretics.

Diaphoretic drugs reduce the temperature by increasing the amount of perspiration and in this way increasing the loss of heat from the skin. As antipyretics I have little experience of the drugs of this class. I have used Pulv. Ipecac. Co along with Antifebrine in a considerable number of cases of Influenza and have found it to have a decided influence on the temperature.

I have also used pilocarpinae Nitras along with the hot dry pack in cases of Scarlet Fever complicated with nephritis and Anasarca, but it was more with the object of inducing active secretion by the skin and thereby reducing the dropsical swelling, consequently no special note was kept of any reduction of the temperature.

5. Specific Antipyretics.

By the term Specific Antipyretics I mean those drugs which have been found very useful for the pyrexia of particular diseases, but which are not of much use in pyrexia from any other cause.

We have examples of this in many well known and valuable drugs, as Salicine and the Salicylates in the pyrexia of Acute Rheumatism, and Quinine in the pyrexia of Ague.

It is not necessary to discuss this class further here as in this paper we are dealing with pyrexia apart from its cause.

(1) Pharmacy, Materia Medica & Therapeutics: Whittle
Fourth Edition page 504.

(2) Lancet. 14th July 1888. page 55.

c. Antipyretics.

The two antipyretic drugs of which I should like to speak are Antipyrine and Antifebrine.

Antipyrine is a drug whose action is not yet fully understood. Whether it has any influence in lessening heat production is not yet known as a fact, but there can be little doubt that it causes increased loss of heat.

(1) Filchene who first investigated its action found "that the temperature falls gradually, often without sweating, and reaches its limit in three or four hours. It remains low for seven or eight hours and may not rise for twenty hours. The rise is not generally ushered in with shivering, as after Kairin. The pulse falls, but the respirations are not materially altered, while blood pressure is slightly increased. Before the temperature falls dilatation of the cutaneous vessels has been observed."

(2.) Dr. McAllister, Cambridge, in the Croonian lectures on Antipyretics, delivered at the Royal College

of Physicians says, "Summing up the results so far enumerated it appears that Antipyrine increases skin radiation, diminishes the difference between peripheral and central temperatures, lowers the temperature as a whole, diminishes thermogenesis, diminishes the production of nitrogenous waste, and therefore nitrogenous metabolism, and frequently, but not always, increases perspiration, while it generally slows the heart and slightly increases the tension of the radial artery."

I have used Antipyrine largely in febrile affections and have found it often of very great value. My experience has been that not only does it reduce the temperature but that it keeps it down for a considerable time after each dose; the patient seems quieter, and in some cases, though by no means in all, the skin becomes moist.

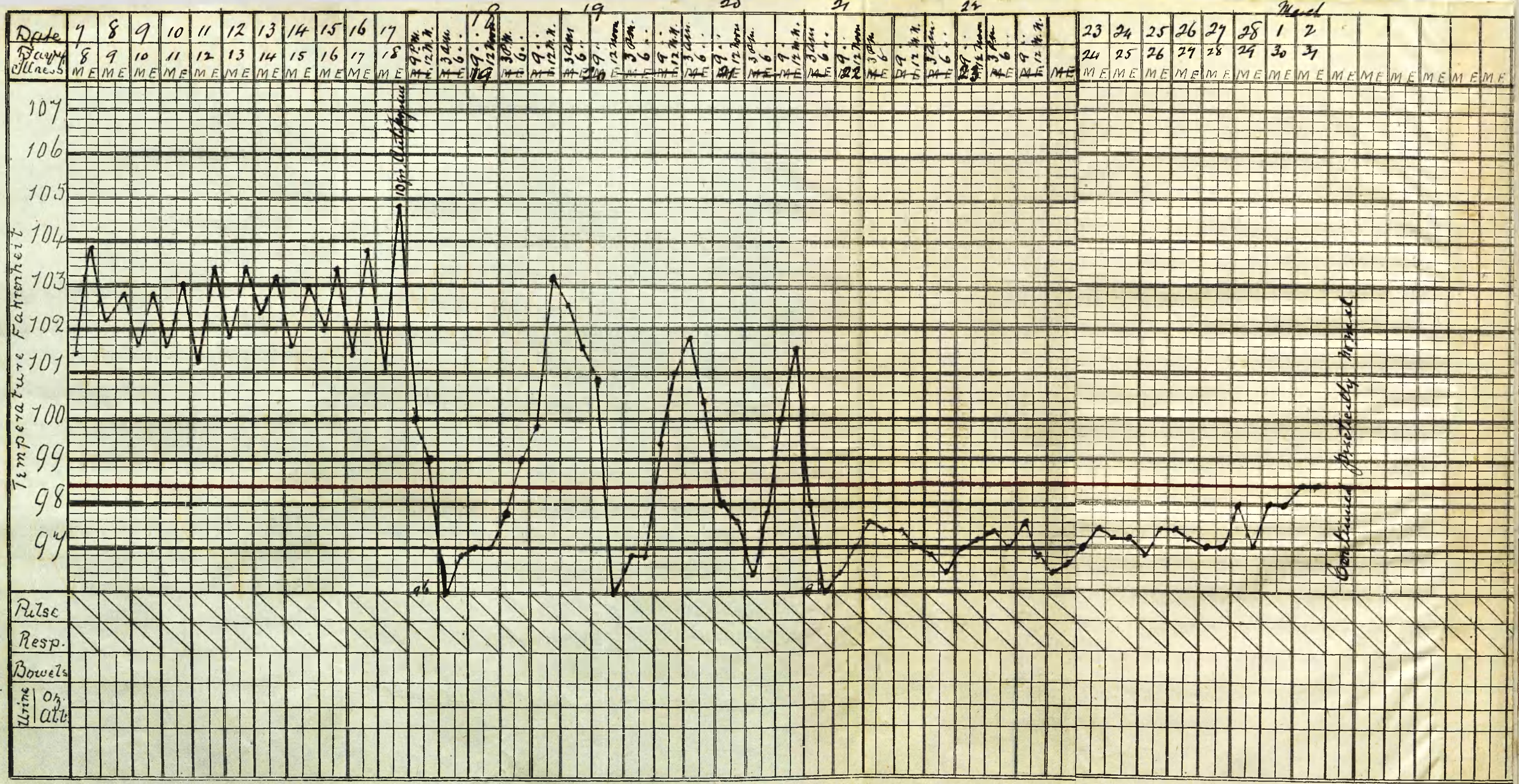
With one possible exception I have never had any serious effect produced by the drug. The exceptional case I mention is one in which there was marked collapse after a single dose of ten grains.

This was the case of W^m. D. aged 14 years, a patient in Belvidere Hospital suffering from Enteric Fever. On the 17th Feby. 1891. (the eighteenth day of his illness) after a very restless day, and no sleep the previous night, and a temperature of 104.8° F. I ordered him ten grains of Antipyrine. I saw him three hours after its administration; he was asleep, his skin was wet with perspiration and his temperature was 100°. I felt quite pleased at the effect produced: but after other three hours the nurse in charge told me that the temperature was 96° and that he seemed quite collapsed. I went to the ward and found the boy in a state of collapse; his nose, ears, and extremities were cold, his pulse was very small and very feeble; in answer to questions he said he felt very well, did not feel at all cold and wondered why he was having so much attention. We got more blankets put over him, hot bottles placed around him, and administered brandy freely; but in spite

February
1891

William Davidson
age 14 years

Enteric Fever



103.8 Rectal

ab

continued prostratedly in bed

of all our efforts the temperature could not be got to rise above 96.8. The temperature remained subnormal for twelve hours but there were no alarming symptoms. Dr. Allan saw the patient in consultation and said "he would have considered it a crisis if Antipyrene had not been given".

Three possible causes occurred to my mind.

- 1. A Crisis
- 2. Intestinal Haemorrhage
- 3 Collapse following Antipyrene.

Opposite is a chart of the temperatures in this case.

That it was not a crisis was proved later on. The temperature afterwards was very irregular; on three separate occasions being above 101° and on four occasions below 99°. After four days the temperature became more uniform but still remained slightly subnormal.

It was not intestinal haemorrhage. There was no trace of blood in the motions which were

(1) Lancet 12th May 1888 page 919

(2) Provincial Medical Journal 1st June 1888
page 283.

passed afterwards. The nurse was warned that there might be blood, and was instructed to watch carefully.

I suppose then we must come to the conclusion that it was the Antipyric. If this be the case it seems to me to be a most peculiar result from one dose of ten grains.

I may say that the patient ultimately recovered and was dismissed quite well.

Antifebrine.

(1) Dr. Park in a paper in the Lancet in May 1888 states as the result of his experience that "Antipyric will be found best adapted for sthenic cases and Antifebrine for asthenic."

(2) Friedlander's observations also go to prove that Antipyric acts better on well kept children than on those who are poorly taken care of.

In the limited number of cases in which I have used Antifebrine, the cardiac depression was certainly not so marked as in those cases in which Antipyric was used, and perspiration was

1891

February

George Mitchell
age 2 years

Measles
Bronch. Pulmonia.



Remains normal.

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a much more constant result.

My experience has led me to the conclusion that Antifebrine is a much better and safer drug than Antipyrine in the cases of children and those with feeble cardiac action.

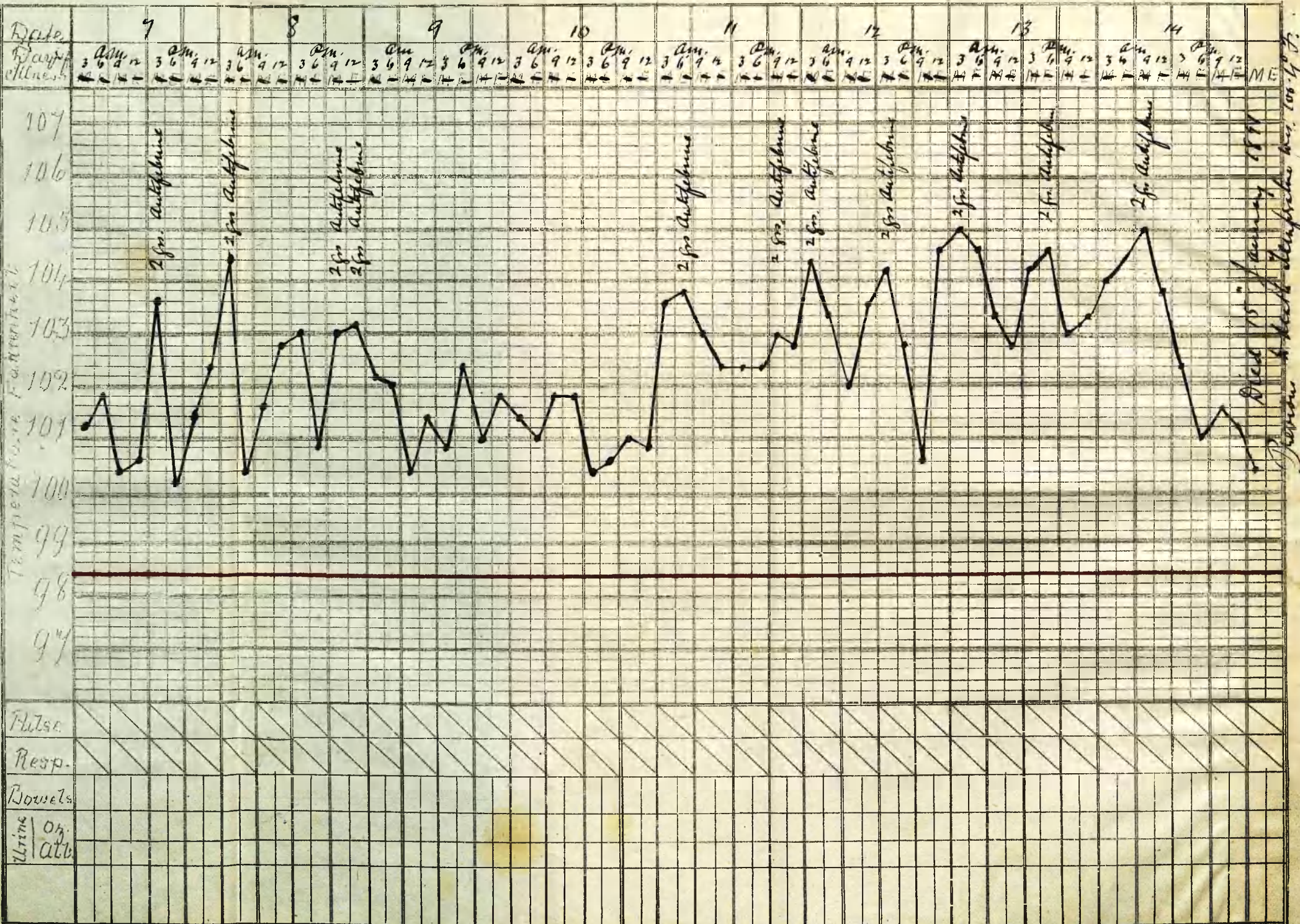
Opposite is the chart of the temperature of a child, S. M. aged 2 years, admitted into Bellevue Hospital suffering from Measles Complicated with Broncho-pneumonia. In this case Antifebrine was given, the dose being one grain. In addition to this the treatment consisted in applying linseed and mustard poultices to the back and chest, and the administration of a stimulating expectorant. The temperature was taken every three hours. The chart shows a marked diminution in temperature after a dose of Antifebrine. It also shows that the temperature did not rise so soon again as it did in the cases I noted where the cold pack was used. One grain of Antifebrine was given when the temperature was 105.4: three hours afterwards it was 104.6

1891

Saunam

John Frank
age 5

Scrub Fever



Died 15 January 1891
 Cause of death unknown age 100 1/2

Six hours afterwards it was 104°. Another dose (one grain) was given and three hours afterwards the temperature was 101.8, and six hours afterwards it was 100°. It then began to rise but did not reach 105° until eighteen hours after the Anti-febrine had been given. Only on two occasions was the temperature the same three hours after a dose of Antifebrine and never was it higher.

The rest of the chart explains itself.

I enclose a copy of another chart which, although the case ultimately proved fatal, shows the good results of Antifebrine.

This is a chart of the temperature of a boy, J. J. aged 5 years, who was admitted into Belvidere Hospital on the 6th Jan. 1891 suffering from Scarlet Fever. In this case the throat was very bad from the first; there was considerable ulceration and sloughing of the tonsils and fauces and death ultimately took place apparently from Septicæmia.

The chart explains itself and shows the depression

in temperature after a dose of Antifebrine which in this case was two grains.

I have all through this paper spoken of febrile temperatures quite apart from the cause.

If the temperature of the body, once it reaches a certain height, becomes a danger to life in itself quite apart from the condition which causes it, then we are justified in guarding against that danger, and in adopting means to reduce the temperature.

However, at the same time, we must by no means neglect the proper treatment of the particular disease which causes the pyrexia.

After considering this subject the opinions I have formed are

1. That cases of moderate pyrexia require no special antipyretic treatment. At the same time the patient may experience great relief and comfort from either cold or tepid sponging.
2. That as an antipyretic the hot dry pack

is not very satisfactory.

3. That the cold pack is a method of reducing the temperature which can only be used in strong robust patients, and even in these cases its effect has to be very carefully watched.

4. That Antipyrine and Antifebrine may be used with advantage in many cases; the latter specially in patients of low vitality.