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Original Article.

OBSERVATIONS ON THE USE OF ANTIPYRINE AND THALLIN IN THE TREATMENT OF TYPHOID FEVER.¹

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IN the autumn and winter of 1885-86, and in those of 1886-87, I ordered antipyrine and thallin in twenty-four cases of typhoid fever in the Massachusetts General Hospital, with the object of ascertaining, as far as possible, to what extent they could be relied upon as remedies of positive value in the treatment of that disease. An abstract of each case was made, and compared with the temperature-chart, the latter including, in a considerable number of cases, the hourly varia-

tions after each dose, as well as the regular morning and evening range. The main points for investigation included:

- (1) The dose of each drug required to produce a depression of two or three degrees of temperature.
- (2) Conditions affecting the action of the drugs.
- (3) Effects on the condition of the patient.
- (4) Effects of the drugs in fatal cases.
- (5) Effects of antipyrine and thallin when given in continuous doses.
- (6) Comparative effects of antipyrine and thallin.

The twenty-four cases include all the typhoids that were submitted to the action of these drugs in the wards under my charge during these two terms of service.

The regular treatment of typhoid fever in these wards was expectant. A considerable proportion of the cases required no special interference. The patients were carefully fed, chiefly with milk, plain or peptonized, and occasionally with animal broths. All were regularly sponged several times daily with plain water, either cold or tepid. In cases where there was much prostration, brandy or whiskey was given, in doses ranging from one to two drachms, every three or four hours, to one ounce every hour. The patients were very lightly covered, often with only a sheet. Very few required opiates.

Antipyrine or thallin were given only when the temperature rose above 102.5° (Fahr.).

DOSE.

The doses employed varied according to the age of the patient, and the degree of pyrexia. From twenty to thirty grains of antipyrine were generally given to an adult, eight grains to a child of twelve years, and five grains to a child of three years, whenever the temperature reached three-and-one-half degrees (Fahr.) above the normal standard. If retained by the patient, this invariably had the effect of reducing the temperature two or three degrees, and sometimes more, in the course of one or two hours; the mercury then rose during the same length of time, till it reached its original level, or a degree below that. The same results followed the use of thallin in much smaller doses. In one case (an adult), two grains reduced the temperature from 105.7° to 101.2°. In general, four grains of thallin were given to an adult. When given in continuous doses, every three or four hours, for example, it was found, in some cases, that after one full dose, much smaller subsequent ones were sufficient to maintain the temperature at a given level. In the case of a patient twelve years old, after one dose of two grains of thallin, a single grain, given from twice to six times daily, was sufficient to keep the temperature at a moderate level.

CONDITIONS AFFECTING THE ACTION OF THE DRUGS.

It was observed that antipyrine and thallin acted most promptly, and with most permanent effect, when given at, or just before the end of the fastigium, thus giving rise to the suspicion that the improvement would have taken place had the medicine not been given. There is no doubt that this suspicion is just, so far as a permanent reaction is concerned. Inspection of the charts shows that, in general, antipyrine and thallin given during the fastigium reduced the temperature promptly, but only temporarily, except when they were given shortly before the lysis began (Susan Hamblet). In one case, however, that of a child three years old (J.

¹ Read before the Association of American Physicians, Washington, June 2, 1887.

H. Frizzell), the fastigium was unusually short, and the chart shows an immediate and permanent reduction after antipyrine had been given. There was no doubt of the diagnosis in this case. In other cases, it seems probable, from inspection of the chart, that the temperature was controlled, or prevented from rising higher, although no permanent depression was effected, though, of course, this could not be demonstrated. In general, however, it was found that the more severe the symptoms, including high fever, the more difficult it was to maintain a moderate temperature by means of antipyrine or thallin. So far as I could discover, there were no other conditions which interfered with their action.

EFFECTS UPON THE PATIENTS.

The general effect of antipyrine and thallin upon the patients was almost always favorable, and no case was observed in which the exhibition of either drug was followed by any worse results than sweating and occasional vomiting. It was noted, in a large number of cases, that the patients slept tranquilly after taking them. No special prostration or exhaustion was recorded. Generally, it is reported that no change took place in the character or rate of the pulse. In many cases, the patient, from being restless or delirious, became tranquil and rational. In almost all the cases, it is reported that the patients were more comfortable after taking the medicine. These effects were more marked and more lasting when the drug was given during the defervescence than during the fastigium, but still they were observed at all periods of the disease. The favorable effects were decidedly more noticeable in children than in adults, and the drugs were remarkably well borne by children.

ANTIPYRINE AND THALLIN IN FATAL CASES.

I examined with care the records of the six fatal cases, in order to ascertain whether the result could be attributed, in any of them, to the refrigerant medicine. The first case was that of Lizzie Prime, domestic, twenty-seven years old, who entered the hospital December 14, 1886, with typhoid symptoms, signs of bronchitic inflammation, a pre-systolic cardiac murmur, and weak pulse. Three days after entrance she had a dose of antipyrine, which was repeated on the two following days, when the temperature became normal, and the medicine was discontinued. During all this time, the weak and irregular condition of the pulse continued. On the eighth day after entrance, signs of œdema of the glottis appeared, and at eight o'clock in the evening the trachea was opened, but no relief was afforded to the dyspnoea, and the patient died soon afterwards. Although no unfavorable effects following the administration of the antipyrine were recorded, I cannot but think that the condition of the pulse was such that the case was an unfavorable one for the exhibition of the drug. As no autopsy could be obtained, the cause of death could not be certainly ascertained: since the trachea was opened before death, œdema of the glottis could not have been the only cause. Stimulants were freely given throughout the case.

The next fatal case was similar to the last in respect to the condition of the pulse. Joseph Farrell, twenty-six years old, waiter, entered the hospital October 1, 1886, and died October 11th. He had been in bed seven days before entrance. He took several doses of antipyrine, of five to ten grains each, daily for nine

days, after which the temperature gradually fell to 99° on the day of his death. Throughout the case, the action of the heart was very feeble, and the lungs were œdematous. The density of the urine was 1012; there was a trace of albumen, with numerous hyaline and granular casts. *Post-mortem*, the muscular substance of the heart was found to be pale and translucent; the kidneys, on section, were pale, the cortex thickened, glomeruli distinct, and surrounding substance gray; spleen about four times the natural size, soft, and easily torn; great increase of pulp. The intestines showed the usual lesions. Stimulants were freely given throughout the case. No unfavorable symptoms which could be attributed to antipyrine were recorded, but the case was evidently not likely to be benefited by it.

The third fatal case, that of Louisa Smith, twenty-six years old, was one of relapse. Her mother and sister had typhoid recently, each had a relapse, and each had internal hæmorrhage. Her husband, also, was convalescent from a "fever." The patient, who was much fatigued from nursing the others, and who also had a miscarriage at the fifth month, eight weeks previously, entered the hospital February 6, 1887, having been in bed two weeks with typhoid symptoms. The case was of moderate severity, and without special treatment the temperature gradually fell, and reached the normal standard on February 13th, the twenty-first day of the disease. February 17th, the temperature began to rise again, and after four days it reached 104°. On the sixth day of the relapse, one dose of thallin of four grains was given, which appeared to have a favorable effect, and was not repeated. February 28th, the eleventh day of the relapse, at 7 P. M., a sudden rigor occurred, with intense pain in the abdomen, vomiting, thready pulse, and all the symptoms of peritonitis from perforation, of which the patient died, March 3d, at 7 A. M. As only a single dose of thallin was given, which was followed by no unfavorable symptoms eight days before death from perforation, it is not probable that the drug had any influence in causing the fatal catastrophe.

Kate Murphy, twenty-one years old, entered hospital February 21st, and died, March 6, 1887. This was the fifth case of typhoid fever brought to this hospital from the same house, and the eighth person who had contracted the disease there, this season. Pale, chlorotic-looking; in bed three days before entrance. Temperature at entrance, 103.4°. It rose to 105.7° on the evening of February 25th, (eleventh day), and began to fall on the morning of the 27th, (thirteenth day). The decline continued till the evening of March, (nineteenth day), when it was at 98.5°. During all this time the symptoms grew worse and she died early the next morning. The cause of the failure of this patient appeared to have been diarrhoea, which set in on the fifteenth day, and was followed by delirium and exhaustion. She took six doses of thallin of two grains each, the last one seven days before her death.

Margaret Coffin, aged 54, entered the hospital October 16, 1886, and died November 11th. For six weeks before entrance she had been occupied in nursing a daughter with typhoid, and another daughter entered along with the mother, sick with the same disease. The symptoms began two weeks before entrance, and were threatening from the first. The temperature was very irregular, and at times as low as

97° without obvious cause—there was no hemorrhage. Diarrhoea was persistent. Treatment was chiefly by free administration of stimulants. November 6th, two grains of thallin were given at 5 A. M., the temperature being at 103°; it began to fall at once, and 8 o'clock was at the normal point. In an hour it rose rapidly to 102.2° and the dose was repeated. The next day the same dose of thallin was given at 10 A. M., with a similar result. No more was given, although the patient seemed more comfortable after the medicine. She gradually failed, and died at 2 A. M., November 11th, at about the thirty-sixth day of the disease.

The sixth fatal case was that of William Millis, twenty-four years old, who entered the hospital November 17th, and died November 25, 1886. In bed five days before entrance. He steadily grew worse until his death. The symptoms were stupor, delirium, and prostration. There was no evidence of serious lung or heart complication; but the condition of the urine was suspicious of previous renal disease. Thallin and antipyrine were thoroughly tried throughout the course of the disease, the former in doses of four grains, which readily reduced the temperature several degrees, though only for a short time. Antipyrine was given several times in doses of fifteen and twenty grains, smaller doses failing to act. Thirty grains were also given by enema twice, but without any effect at all. On the whole, the general effect of the antipyretics was thought to be favorable, it being noted repeatedly that after a dose had been given the patient was less restless, and more comfortable, notwithstanding a chill often occurred.

CONTINUED USE OF ANTIPIRETICS.

A few cases of typhoid were treated by the continued administration of antipyretic remedies. Either a single dose was given daily, or, as in most cases oftener than once daily. As an example of this method may be cited the case of John Swift, twenty-nine years old, who entered the hospital December 14, 1885, complaining for two weeks of lassitude and loss of appetite, and for one week of diarrhoea. The chart shows that the fastigium was just beginning at the time of his entrance. The temperature was 103°, and later the same evening 103.4°. He was much prostrated, and stupid, had abundant rose spots, enlarged spleen, gurgling in the right iliac region, etc. The next day he was delirious, trying to get out of bed, and twenty grains of antipyrine were given, after which he perspired freely, and became much quieter. The temperature was reduced from nearly 105° to 101°. After that he got two doses daily, of the same amount, except on one day when none was given; and it is remarkable that on that day only did the temperature rise above 103°. During the rest of the fastigium it varied between 101° and 102.5°. At the end of eight days the defervescence began, the temperature falling gradually and spontaneously, during five days, when it became normal, on December 31st, at about the twenty-fifth day of the disease. It is reported that he never had nausea or vomiting; the pulse remained unchanged after antipyrine; restlessness and delirium were much diminished.

In one case in which the temperature rose during the fastigium to 106° small doses (one and two grains) of thallin and antipyrine, sometimes one and sometimes the other, were given in a series of thirty-four doses, at intervals of from one to eight hours, with a

single dose of thirty grains of antipyrine, without unfavorable effect, and the patient recovered.

COMPARATIVE EFFECTS OF ANTIPIRYNE AND THALLIN.

The study of the reports of the cases and of the temperature charts reveals but little difference in the effects of the two drugs; but soon after the introduction of thallin it was almost always employed in preference to the other, and the general impression derived from my experience in the two is that prolonged chill, excessive sweating, and vomiting were more frequently observed after the employment of antipyrine than of thallin.

CONCLUSIONS.

So far as trustworthy conclusions can be obtained from the comparison of so small a number of observations they would seem to be as follows:

(1) Antipyrine and thallin given internally have a remarkable power of reducing by several degrees the bodily temperature in typhoid fever within a period of from one to three hours, after which in most cases the temperature rises again in about the same length of time, sometimes to the original degree, but often not quite so high.

(2) The use of the drugs did not appear to give rise to any unfavorable effects upon the course of the disease, even in fatal cases.

(3) In general, the condition of the patient was more comfortable after the effect of the refrigerant medicine was produced; he was more tranquil, often slept, and frequently expressed himself as relieved.

(4) The refrigerant medication by antipyrine and thallin appears to have no specific or decided effect upon the course or issue of typhoid fever. In some cases the general condition was apparently relieved or improved throughout the course, but in most cases these drugs can only be looked upon as palliatives, often contributing to the patient's comfort, and perhaps indirectly promoting his safety.

(5) The failure of such efficient antipyretics as antipyrine and thallin to avert the fatal issue in many grave cases of typhoid fever shows that the danger does not consist in high temperature alone, but that the latter is rather an index of the abnormal condition which we call fever, though probably adding somewhat to the danger.

(6) By the internal use of antipyrine and thallin all the effects which are claimed for the treatment of typhoid fever by the cold bath are readily obtained without the trouble and inconvenience of the latter method, and without exposing the patient to the danger of exhaustion and shock consequent on the fatigue of removal from bed.

(7) These remedies may be given without danger to the youngest patient in suitable doses, and indeed their beneficial effects are more decided with them than with adults.

ADDENDUM.

Before concluding this paper, I wish to allude to the very favorable effect of refrigerant medicines in the treatment of the hectic of pulmonary consumption. Eight grains of antipyrine given daily at three or four o'clock in the afternoon has in my experience both in hospital and private practice been effectual in preventing the rise of temperature, the sweating and the flushing which are a source of so much discomfort to phthisical patients, especially during the period of soften-

ing, although the remedy appears to have no effect on the progress of the disease.

The chart which I will pass around, is that of F. W. Tolsom, eighteen years old, who entered the hospital January 23, 1886, with cough and muco-purulent expectoration, night sweats, loss of weight and strength, etc. The signs were dulness, broncho-vesicular respiratory murmur, bronchophony, moist crepitant râle, etc., in the right apex, extending in front to the third rib, and half way down the scapula behind. One dose of antipyrine was given the next day, but none on the two following days, during which the evening temperature ranged between 103° and 104°. Eight grains were then given daily at 4 P. M., for the remainder of his stay (13 days), during which time the temperature was greatly reduced and the hectic suppressed. The patient also gained two pounds in weight.

Clinical Memorandum.

ATTEMPTED SUICIDE FROM THE INGESTION OF FIFTY-ONE GRAINS OF MORPHINE, THE GREATER PART OF WHICH REMAINED IN THE STOMACH THIRTEEN HOURS: RECOVERY.

REPORTED BY GEORGE M. MORSE, M.D., OF CLINTON, MASS.

In the JOURNAL of May 12th is reported "A Case of Attempted Suicide by the Ingestion of Thirty-six Grains of Morphine, which remained in the stomach five hours." I have to report a still larger amount taken, and remaining a still longer time in the stomach.

May 25th, M. C., aged thirty-two years, was found by his boarding-mistress, at ten minutes past twelve, in his room, on the bed, unconscious. Dr. French was called, who sent for me, with the request that I would come immediately, and bring a stomach-pump. I arrived at the house at about 1 o'clock, P. M. We found the patient, a strong, well-built man, dressed with the utmost care and nicety, lying on the bed, which had not been slept in, unconscious, sweating profusely; pupils contracted to a pin's point; respiration very irregular, abdominal; lips purple, face cyanotic. On the table was found a bottle with Power's and Weightman's red label, containing, by weight, nine grains of morphine: in a goblet by side of bed, about two drachms of water, which tasted like a solution of morphine; also a sealed letter, directed to patient's wife, marked "deliver immediately—death." The bottle was apparently a new bottle, fresh from the apothecary; the tin-foil had not been entirely removed from the cork. In a vessel under the bed was found, as we judged, about two ounces of greenish fluid, containing food, the green color given, apparently, by garden-rhubarb. A lamp was burning in the room, indicating that the patient had been on the bed many hours. The lamp would ordinarily burn for twelve or fourteen hours; the oil was nearly exhausted.

The diagnosis was easily made out, namely, attempted suicide by the use of morphine, taken sometime during the previous night. Attempts, which were ineffectual, had been made by Dr. French to make him swallow coffee. He had also administered atropine hypodermically. While getting my stomach-pump ready, one-thirtieth-of-a-grain of atropine was injected. At 1.15 P. M., I removed ten ounces of

fluid, like, in appearance, the liquid found in the vessel, pumped back sixteen ounces of warm water, which I removed, and injected another pint of water, and removed that also. Having thoroughly rinsed out the stomach, I pumped in a pint of very strong black coffee. Flagellation of the face by a wet towel, and of the nates by a small cane, was kept up until a galvanic battery was obtained, one pole of which was applied to the epigastrium, and the other to the carotid triangle.

2.30 P. M. Pupils dilated a little; respiration improved; patient not so cyanotic. Flagellation caused corrugation of the superciliary and orbicularis muscles.

3.30 P. M. Patient very purple, entirely unconscious; pulse 140, respirations three per minute. We gave ten grains of caffeine. Galvanism was continued; the negative pole applied to lips and carotid triangle alternately. 5 P. M. Respiration improved; Cheyne-Stokes in character.

5.30 P. M. Caffeine, ten grains; galvanism continued.

6 P. M. Pulse 148, respirations twenty per minute.

9 P. M. Patient could be made to open eyes by shouting, shaking, and by applying the cane with considerable force to the nates. Caffeine every three hours; also galvanism intermittently.

2 A. M. Nurse said he waked up and became conscious. 9 A. M. Patient seemed quite conscious, but said his head felt light; vomited, and in the afternoon was quite delirious, saw snakes, etc.

He was well the next day, and gave this account of himself: At 11 P. M., May 25th, he retired to his room, took a bath, dressed himself in his best clothing—clean shirt, collar, white neck-tie, and white stockings—wrote the letter to his wife; put one-half the contents of an eighth-ounce bottle of morphine (which he had bought some days before) into a goblet of water, and drank it; filled the goblet with water and put more morphine in it, and drank of it occasionally until he became unconscious; the last drink he took made him sick, and he vomited once—what we found in the vessel.

There were nine grains found in the bottle, showing that he had taken fifty-one grains, and he said he wasted only what he vomited, and which we found in the vessel. According to his account, he drank about twelve ounces of water, in which were dissolved fifty-one grains of morphine. He vomited two ounces, so that there must have remained in his stomach for more than twelve hours more than forty grains of morphine. No estimate is here made of the contents of his stomach before taking morphine. There must have been considerable, as we found what appeared like garden-rhubarb in the matter pumped out.

It is to be regretted that no attempt was made to ascertain the amount of morphine pumped out, but, in the hurry and confusion, the whole was thrown away. The points of interest in this case are the large amount of morphine taken, the length of time it remained in the stomach before any attempt was made to remove or antagonize its effects, and lastly, the success of the treatment, namely, the stomach-pump, atropine, caffeine, galvanism, and flagellation.

This case, together with the case reported from Denver by Dr. Fisk, shows that however desperate the case may seem to be, however large the amount taken, or the length of time before treatment is commenced, persistent endeavors to relieve the patient