CLINICAL OBSERVATIONS ON THE ACTION OF ANTIPYRIN AND THALLIN.

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THE following observations on the action of Antipyrin and Thallin were made at the suggestion of Dr. Ringer on patients admitted under his care into University College Hospital. My main object has been to investigate the utility of these drugs in the treatment of acute articular rheumatism, and to compare their action with that of Salicylate of Soda. Notwithstanding the voluminous literature on this subject which has appeared during the last few years, further observations would seem to be desirable when we consider the somewhat conflicting opinions at which different observers have arrived. After the admission of a case of acute rheumatism, no drug, or merely a placebo, was given for the first twelve or twenty-four hours. By so doing any error due to the simple effect of complete rest on the temperature was as far as possible avoided. The fall of temperature from this cause is often not inconsiderable, amounting in some cases to one or two degrees Fahrenheit. Dr. Ringer points out that the first temperature taken after admission is often the highest. The administration of the drug was then commenced, and in those cases in which it did not appear to be beneficial it was followed by the administration of the salicylate of soda. The following are brief details of some individual cases:—

Cases of Acute Rheumatism treated with Antipyrin.

CASE 1.—T. R.—, aged twenty-two, was admitted on Oct. 12th, 1885, with his first attack. The right elbow and wrist were swollen, red, and very painful, and the left shoulder was painful on movement. There was a faint systolic murmur at the apex. During the twenty-four hours after admission the temperature varied between 100° and 101·4°. At 3 P.M. on Oct. 13th (day after admission) twenty grains of antipyrin were given, and repeated at 4 P.M. and 5 P.M. The temperature fell gradually from 101·4° at 3 P.M. to 98·4° at 12 P.M.; the physical condition of the joints remained the same, but the pain was rather less. On the following day at 11 A.M. the temperature had risen to 100·4°; twenty grains of antipyrin were given, and repeated every two hours until 6 P.M., the result being a fall to 98° at 7 P.M., without the slightest effect on the symptoms. At 3 A.M. on Dec. 15th the thermometer rose slowly to 99·8° at 11 P.M. At 11 A.M. on the following day twenty grains of salicylate of soda were given, and repeated at intervals of two hours. The result was a fall from 99·8° at 11 A.M. to 97·8° at 3 A.M. on the following morning (Oct. 17th), when "the pain had all gone" and the swelling subsided. The temperature remained normal, and recovery was rapid. In this and all other cases the salicylate was continued in gradually diminished doses until at least one week after the temperature had fallen to normal.

CASE 2.—F. J.—, aged seventeen, was admitted to the hospital on Dec. 7th, 1885, with his first attack. Both wrists and both knees were swollen and painful, the right shoulder was painful, and there was a soft systolic murmur at the mitral area. The temperature at 3 P.M., shortly after admission, was 102·2°; it fell to 99·8° at 11 A.M. on Dec. 8th without treatment, and at noon was 100·2°. Twenty grains of antipyrin were then given, and repeated hourly until 6 P.M. Two hours after the first dose the temperature was 99°, and fell quite uniformly to 96° at 10 P.M. The pulse fell from 66 to 60. There was no increase of sweating, and no prostration; the symptoms remained unchanged. The temperature rose to normal at 11 A.M. on the following day, and the antipyrin was not repeated. The joints were rather less painful, and the right wrist less swollen. On the following day at noon (temperature 98·4°) twenty grains of salicylate of soda were given, and repeated every three hours. Towards evening the pain became much less, and the next morning was gone, and all swelling had disappeared. The temperature remained normal. During his stay in the hospital signs of slight aortic disease developed, but no cardiac symptoms were present.

CASE 3.—F. B.—, aged nineteen, was admitted on Dec. 1st, 1885, with his second attack. The left elbow and

wrist and the left knee and ankle were affected. The temperature at 11 P.M. (twelve hours after admission) was 101·8°. Twenty grains of antipyrin were administered, and repeated at 12 P.M. and 1 A.M. The temperature fell slowly to 99·2° at 7 A.M. on Dec. 2nd. The right elbow and wrist had during this time become swollen and painful, so that the antipyrin was not repeated; but at 3 P.M. salicylate of soda was ordered in twenty-grain doses every two hours, with a resulting fall to normal at noon on the following day, and a complete alleviation of the symptoms. On admission a systolic murmur was audible at the apex, and on Dec. 5th a diastolic murmur was for the first time heard at the base; but there were no cardiac symptoms, and on Dec. 16th the patient left the hospital quite well.

CASE 4.—H. S.—, aged thirty-one, admitted on Oct. 8th, 1885, with his second attack. Right wrist and both knees and ankles affected. No signs of heart affection. At 11 P.M. on the day of admission the temperature was 102·6°. At 3 A.M. on the following morning the salicylate of soda was commenced in twenty-grain doses every two hours, with a resulting fall to 99·4° at 7 A.M. The symptoms were, however, scarcely affected. On the following day severe headache and buzzing in the ears having developed, the salicylate was only given every four hours. The temperature on the 12th rose again to 102°. During the fortnight after admission this treatment was continued without success, and the swelling of the knee-joints became very great. Blistering was tried with some benefit. On Oct. 23rd, at 11 A.M., the thermometer registered 101·6°, and twenty grains of antipyrin were given at 3 P.M., and repeated at 4 and 5 P.M.; at 7 P.M. the temperature was 98·4°. On the following day (Oct. 24th) ten grains were given every two hours. The temperature did not rise above 99·4°. The dose was gradually lessened, and the various affected joints were blistered. On the 28th the swelling of the knees had quite disappeared, and after this the patient made a steady though slow convalescence.

Cases of Acute Rheumatism in which Thallin was employed.

CASE 1.—E. S.—, aged thirty-five, was brought to hospital with her second attack on Dec. 29th, 1885. Both wrists, both ankles, and the left knee were affected. The temperature on admission was 100·2°; at 1 P.M. on the following day, 102·6°. Thallin was then commenced—one grain of the sulphate every hour. The temperature fell steadily to 100·6° at 6 P.M., and then rose to 101·6° at 9 P.M. At 10 P.M. the dose was increased to two grains hourly, after which the temperature fell with slight fluctuations to 98·8° at 9 A.M. on the following morning (Dec. 31st); it then began to fluctuate between 98·8° and 100·4°. (The temperature was taken hourly.) The symptoms were absolutely unchanged. At noon the dose was increased to three grains hourly, and at 4 P.M. 99° were registered. After the next four doses the patient vomited, so that the drug was stopped at 8 P.M., the temperature standing at 100°. At 3 P.M. on the following day the salicylate was commenced in twenty-grain doses every two hours. The same evening the symptoms were much lessened, and on the next morning they had disappeared and the temperature was normal. The patient made a rapid recovery. No cardiac complications developed.

CASE 2.—J. T. G.—, aged twenty, was admitted on Dec. 21st, 1885, with his first attack. Had right hemichorea when fifteen years old. Both knees and ankles and right shoulder affected. Apex systolic murmur, and pericardial rub audible. Temperature on evening of admission 102·8°; at 11 A.M. on next day, 102·2°. Thallin then commenced, one grain hourly. Temperature at 6 P.M. 100·8°; at 11 P.M., 101·4°. Dose increased to two grains hourly. The temperature fell uniformly to 98·8° at 2 A.M. on next morning (Dec. 23rd), and then rose with considerable fluctuations to 101·6° at 8 A.M. No improvement was noticed in the symptoms, and both wrists had become swollen and painful. The thallin was stopped at 8 A.M., and at 8 o'clock P.M. the thermometer stood at 102·4°. The salicylate of soda was then given—twenty grains every two hours. At 3 A.M. on the following morning the temperature was normal, and at 11 A.M. the patient expressed himself quite free from pain, and the swelling had entirely subsided. The pericardial rub disappeared on the third day after admission, and no fresh murmurs presented themselves. He was discharged on Jan. 5th. During the administration of the thallin the urine assumed a dark clive-green colour and smelled strongly of

the drug. Ferric chloride gave a dirty-brown precipitate soluble in excess to a dark reddish-brown solution. This effect on the urine was almost constantly noted. It rapidly disappeared when the drug was stopped.

CASE 3.—S. G.—, aged forty-five, was admitted on Dec. 18th, 1885, with his third attack. There was affection of both elbows and wrists, and to a less extent of the knees and shoulders. Temperature on admission 102.2° ; at 9 A.M. on the following morning, 101.4° . One grain of sulphate of thallin was given every hour, until 6 P.M., when the temperature was 99° . It was then stopped on account of the great nausea it produced and the copious sweating which occurred. It had no effect on the joint symptoms. At 11 A.M. on the next day twenty grains of the salicylate were ordered every two hours; the temperature was then 99° , and was normal three hours later. Rapid removal of symptoms followed and recovery was uninterrupted.

Professor Dujardin-Beaumetz of Paris, after an extensive trial of antipyrin, concluded that when used in acute rheumatism it brought down the fever, but did not materially affect the joint symptoms. Many other observers, including Neumann of Berlin,¹ and Pribram,² have considered the drug equal to the salicylate in rheumatic fever. My own experience, although very limited, certainly coincides with the first opinion—viz., that antipyrin cannot claim any specific action in rheumatism. An important fact clearly brought out by the above cases is that after the temperature has been reduced to normal by the antipyrin, the other symptoms of the disease are rapidly removed by the administration of the salicylate; this, it seems to me, indicates a marked difference between the former, which merely removes one symptom of the disease—viz., the fever,—and the latter, which appears to strike at the root of the mischief. Case 4 is an example of those unusual cases in which the sodic salicylate failed. Here antipyrin appeared of some service, and in such cases, as well as in those attended with hyperpyrexia, the drug deserves further trial. In none of the cases of rheumatism in which antipyrin was given did it produce any of the toxic effects—vomiting, prostration, &c.—which have been described as resulting from its use, and some of which have occurred in cases at University College Hospital. With regard to thallin, the general opinion of those who have employed it seems to be that it compares very unfavourably with salicylate of soda in the treatment of acute rheumatism. Thus, Dr. Jaksch³ found that although the fever was reduced by its action, yet the other symptoms all remained. The above cases tend to confirm this conclusion. The considerable extension of the disease which occurred in Case 2 during the exhibition of the drug, notwithstanding the lowering of the temperature, would be inexplicable were we to believe that the antipyretic effect was due to any influence of the thallin on the disease process itself. The frequently repeated doses necessary, and the very transient effect produced, compel us to consider thallin very inferior to antipyrin, notwithstanding slight advantages, such as rapidity of action, which it may possess. We must therefore conclude that salicylate of soda remains *par excellence* the cure for acute rheumatism, but that antipyrin may be useful in those rare cases in which it fails to exert its apparently specific action on the disease.

I will now proceed to give brief details of a few cases of Phthisis in which Thallin and Antipyrin were employed.

CASE 1.—C. Q.—, aged seventeen years and a half, was admitted on Oct. 10th, 1885, with a severe attack of hæmoptysis. He had had a cough for nearly three months, and once before had spat blood, on Sept. 30th. He had several attacks of hæmoptysis during the few days after admission, and was treated with ergotine, gallic acid, &c. There was evidence of consolidation at the right apex. During the week after admission the average morning temperature was about 102° and the evening temperature between 102° and 103° . On Oct. 19th, at 11 A.M. twenty grains of antipyrin were given, and repeated at noon and 1 P.M. There was a fall from 101.4° at 11 A.M. to 98.4° at 1 P.M. At 12.30 A.M., the temperature having risen to 100.2° , ten grains of antipyrin were ordered every three hours. This was continued for two days, and the thermometer only once registered 100° , standing usually at 99° . On the day after it was stopped the evening temperature was 102° . On Oct. 26th three hourly doses of from ten to twenty grains were given. The temperature fell from 102.6° to 99.2° in five

hours. Shortly after the third dose the patient became very collapsed, the extremities very blue, the pulse small and fluttering, and there were marked tremors in the limbs. This condition lasted about an hour, and he gradually revived after brandy with ammonia and ether had been given freely. Fifteen hours after the last dose the temperature was 96.4° , and then slowly rose, without shivering, to 100.2° during the next seventeen hours. Death occurred on Oct. 30th, and the necropsy revealed extensive disease of both lungs. During the few days that antipyrin was given in ten-grain doses every three hours the night sweats were certainly lessened, but no other improvement was evident in the general condition.

CASE 2.—D. W.—, aged twenty-one, was admitted on Jan. 18th, 1886, with a history of severe cough, rapid wasting, and night sweats of five weeks' duration. There was evidence of consolidation and small vomicae at both apices. During the three days after admission the morning temperature was 101.2° , 100.4° , and 100.4° , and that of the evening, 103.8° , 102.8° , and 103.6° . On Jan. 22nd, at 6 P.M. 105.2° was reached, and at 7.30 P.M. thallin was commenced in one-grain doses every hour; this was doubled at 10.30 P.M. At 5 A.M. on the next day the temperature was 99.4° , and rose rapidly, with severe shivering, to 105° at 9 A.M., although thallin was continued. During the day the lowest record was 100° , and the highest was 105° . At 12 P.M., with violent sweating, the temperature fell to 98.4° , and the thallin was stopped on account of vomiting. In four hours a rise of 5° occurred. During the next three days variations between 102° and 104° were registered. On Jan. 27th, at 10 A.M. (temperature 102°) twenty grains of antipyrin were administered, and repeated at 11 A.M. and noon. The thermometer at 1 P.M. was 97.2° . A rise without shivering followed, 104.2° being reached at 7 P.M.— 7° in six hours. The drug was then ordered in twenty-grain doses every four hours. This was increased on Jan. 30th to twenty-grain doses every three hours, and continued until Feb. 5th. The chart during this time showed great daily variations—from 97° and 99° in the morning to 103° and 104° in the evening. The sweating was increased, but no other ill effects were noted. Stopping the drug had a marked effect on the temperature chart, which showed that although the evening rise remained the same (103° – 104°), the morning fall was about 2° less (100°). The lung disease rapidly extended, symptoms of peritonitis and persistent diarrhoea set in, and the patient died on Feb. 27th. Cavities at the upper part of both lungs were found; there was general peritonitis and extensive tubercular ulceration of the small intestine.

CASE 3.—H. G. F.—, aged twenty, had suffered from severe cough and night sweats, and had been wasting during the three months before his admission on Dec. 31st, 1885. There were signs of a considerable cavity at the apex of the left lung, and consolidation of the right apex. Expectoration profuse, muco-purulent. Patient very weak and emaciated. Morning temperature during first three days in hospital 100° – 101° ; evening, 102° – 103° . At 11 A.M., on Jan. 3rd, 1886, thallin was commenced in one-grain doses hourly. At 5 P.M. the temperature was 98° , and at 9 P.M. 103.4° . Similar fluctuations continued, and on Jan. 5th the dose was doubled. The result was a temperature varying between 98.4° and 101.6° . At 11 P.M. on Jan. 6th the thallin was stopped, and the temperature rose in four hours from 100° to 103.6° . On Jan. 12th, three fifteen-grain doses of antipyrin were given at intervals of one hour. The temperature fell from 101° at 11 A.M. to 99.8° at 3 P.M., and then rose to 101.6° at 5 P.M. On Jan. 13th fifteen-grain doses were ordered every four hours. On the next three evenings 101° were registered. After this, until Feb. 25th, the morning temperature was usually normal, and the evening about 99.6° , rarely touching 100° . On three consecutive days during this time no antipyrin was given, and the evening temperature reached 101° . The general condition improved, the night sweats became very slight, and the expectoration less abundant. The cavity at the left apex showed distinct signs of drying up, the râles became much fewer, and the upper intercostal spaces became depressed. On Feb. 25th the patient left for Eastbourne, much improved, and having gained several pounds in weight during his last month in the hospital. During several weeks after leaving the hospital he continued to take three fifteen-grain doses of antipyrin daily. Whilst he remained under observation the evening temperature varied between 99° and 99.6° .

With regard to thallin it may be stated that in the above

¹ Klin. Wochenschrift, Sept. 14th, 1885.

² Prager, Medicinische Wochenschrift, Oct. 1884.

³ Wien Med. Wochenschrift, 48, 1884.

and other cases of phthisis in which it was employed no appreciable benefit resulted. The almost constant effect on the temperature was a great increase of the daily variations, the minimum temperature being often lowered by 2° or more, whilst the maximum remained the same. Each fall of temperature was accompanied by sweating, and each rise frequently by shivering, and not rarely by distinct rigors. These necessarily added considerably to the discomfort of the patient. I can find no records of cases of phthisis benefited by the use of thallin. The very good result obtained by the continued administration of antipyrin in the last case recorded above agrees with similar results obtained by other observers. In the *Practitioner* for May, 1885, Dr. Holland, of St. Moritz, gives details of several cases which were materially improved by the use of antipyrin, after quinine, salicylic acid, digitalis, and other antipyretic drugs had failed. In one of his cases vomiting was produced. Two similar cases were described in a paper read by Dr. Macalister before the Cambridge Medical Society on August 7th, 1885. The sweating produced was counteracted by the use of minim doses of the solution of sulphate of atropine. In my case the sweating was greatly lessened, and cases recorded by Huchard showed a similar result. In Case 1, recorded above, some slight benefit was derived from the administration of antipyrin, but in three other cases, of which I have notes, no benefit was obtained. The conclusion to which we are led seems to be that the effects of antipyrin in phthisis vary in different cases. In some it acts no better than thallin, and merely lowers the temperature without improving the general condition of the patient or retarding the course of the disease; whilst in other cases it is of great benefit—lowering the temperature, lessening the night sweats, and improving the nutrition. Whether the antipyrin thus acts by merely removing those conditions which are secondary to long-continued fever, or whether it has any more direct action on the disease-process, remains to be shown. The hæmostatic action which has been attributed to antipyrin by several experimenters has suggested a possible further recommendation for its use in phthisis when accompanied by hæmoptysis. It may perhaps be worth mentioning that in Case 1 the severe hæmoptysis was not apparently lessened by full doses of antipyrin.

The most important difference between these two drugs, which is demonstrated by almost all the cases in which they were used, is in the duration of their effects. The lowering of the temperature produced by antipyrin lasts usually for many hours. In one instance the temperature did not rise above 98.6° for thirty hours after the drug was stopped. The rise is gradual and occupies several hours. Thallin, on the contrary, produces a very transitory effect, the rise often beginning within two hours after stopping the drug. This rise is very rapid, and hence is often accompanied by shivering. The influence of antipyrin and thallin on the pulse and respiration appears to me to be very slight. The pulse is usually only slowed by a few beats per minute. In one case, in which antipyrin produced a fall of temperature from 100.2° to 96° , the pulse was only slowed by four beats per minute, and the rate of respiration was unaltered. The experiments of Dr. K. Bettelheim, made in the laboratory of Professor v. Basch at Vienna, led him to a similar conclusion. Professor Pribram,⁴ however, considers that antipyrin has a marked effect on the pulse and respiration.

The various toxic effects produced must now be briefly considered. Vomiting has been frequently noted after the use of antipyrin; much more rarely after thallin. In two cases at University College Hospital antipyrin produced severe vomiting: once in a girl aged twelve years suffering from typhoid fever, after fifteen-grain doses; once in a case of phthisis after twenty-grain doses. The same symptom occurred after the administration of thallin in three-grain doses to a patient with rheumatic fever, who was similarly affected by salicylate of soda. In one other case, nausea, but no vomiting, followed the drug. During the administration of these drugs symptoms of collapse were carefully watched for. In the first case of phthisis detailed above, marked prostration followed the use of antipyrin in three doses of ten, twenty, and twenty grains respectively. Similar symptoms were observed in a boy to whom three fifteen-grain doses were given at intervals of one hour. In no case did thallin occasion any prostration. Looking to the literature on the subject, we find reference made by several observers to cases in which

prostration appeared to follow the use of antipyrin. In THE LANCET of Feb. 28th, 1885, a case was recorded by Mr. Blore, of the Leeds Fever Hospital, in which extreme collapse, terminating fatally, followed the administration of antipyrin, and he concluded "that the extreme depression accompanying the fall of temperature was directly due to the action of the drug." The sweating which accompanies the fall of temperature appears to vary considerably in different cases. As a rule it is not marked, and causes no inconvenience, but in the two cases in which antipyrin caused collapse the fall of temperature was attended with very profuse sweating. In their tendency to produce shivering or rigors the two drugs differ. This we should expect from a comparison of the rapid rise following the fall produced by thallin with the gradual rise after antipyrin; and all observers seem agreed that shivering and rigors frequently follow the use of thallin, but rarely of antipyrin. In every case of phthisis in which thallin was employed for any length of time shivering frequently accompanied the rapid variations in temperature. In one instance a severe rigor, lasting nearly an hour, occurred during the use of one-grain doses hourly. The temperature rose from 100° to 104.8° in two hours. In the case of typhoid fever above mentioned a similar effect was produced. One grain of thallin was being taken every hour on the twenty-first day of the disease. The temperature rose from 101.8° at 9 A.M. to 105° at 2 P.M., and at 1 P.M. a rigor commenced, and lasted for thirty minutes. An exanthematous eruption following the administration of antipyrin was first described by Dr. Ernst of Zurich, and has been seen by many other observers. Thallin more rarely causes a similar rash. This eruption occurred in the case of the boy mentioned above, in whom symptoms of collapse followed the use of three fifteen-grain doses of antipyrin. The rash appeared about one hour after the last dose was given. It consisted of small rosy-red spots over the chest and abdomen, and to a less extent on the limbs. On the face and neck the rash was confluent, and closely resembled scarlet fever. It lasted about an hour, and then gradually faded away. The peculiar appearance of the urine in patients taking thallin has been already mentioned, and constantly occurred. It closely resembles that so often seen in the surgical wards from the absorption of carbolic acid.

Taking all things into consideration, it seems to me that the evidence is strongly in favour of antipyrin. Any slight advantages which thallin may possess are more than counterbalanced by the transitory nature of its action, the frequently repeated doses which are therefore necessary, and the great liability to the occurrence of shivering or rigors. This conclusion agrees with that of most German observers. Unless, therefore, future investigations shall disclose some yet undiscovered advantages in thallin, we may, I think, decide to employ antipyrin in preference to it in any case in which a rapid antipyretic effect is desired. Still more is antipyrin to be preferred in cases such as phthisis, where a long-continued use of the drug is necessary. Regarded as a purely symptomatic remedy, the unanimous verdict is that antipyrin is a most efficient agent.

In conclusion, I beg to offer my best thanks to Dr. Sydney Ringer for allowing me the opportunity of carrying out these brief investigations whilst acting as his house-physician at University College Hospital.

THE MORTUARY QUESTION IN LONDON.—At an inquest held on the 21st inst. at Fulham on the body of a domestic servant who had committed suicide, it was pointed out that in this extensive parish there was no public mortuary. In the present case, the body of the deceased, who had been suffering from an infectious disease, had to be taken to the mortuary of the adjacent parish at Hammersmith. Now that the attention of the authorities has been directed to such an anomaly, it is to be hoped that the want will speedily be supplied.

NORTH-WESTERN ASSOCIATION OF MEDICAL OFFICERS OF HEALTH.—At a meeting of the members of this Association on the 19th inst., Dr. Hime, who has had occasion twice to visit M. Pasteur in Paris, delivered an address on M. Pasteur's treatment of persons liable to hydrophobia, and explained the processes of inoculation adopted by that scientist in his experiments. At the conclusion of the address, Dr. Tatham moved a vote of thanks to Dr. Hime, which was seconded by Dr. Wills and cordially passed.

⁴ Prager, Med. Woch., October, 1884.