THE REACTION OF PATIENTS WITH TYPHOID FEVER TO THE ADMINISTRATION OF ASPIRIN

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For many years the medical staff of the City Hospital for Infectious Diseases, Cape Town, have recognized the occurrence of a severe reaction following the administration of aspirin to patients with typhoid fever. This reaction, characterized by a sudden fall in temperature to subnormal levels, collapse, sweating and bradycardia, is far in excess of the usual antipyretic and diaphoretic action of the drug. When a case was encountered recently in Groote Schuur Hospital, reference to the available literature on typhoid fever failed to reveal any detailed record of a reaction of this kind.

Vincent and Muratet (1917) made the observation that as little as 1 g. of Cryogenine (phenylsemicarbazide) produced collapse with sweating and bradycardia in some patients with typhoid fever, and Nelson and Pijper (1951) decry the use of aspirin and other antipyretics because of the transient fall in temperature they produce by sweating, which leaves the patient considerably weakened. Knight *et al.* (1950) found bizarre temperature charts in patients with typhoid fever who were given antipyrine or quinine. Other authors (Gay, 1918; Byam and Archibald, 1922; Osler and Macrae, 1920; Ker, 1911; Harries and Mitman, 1953) recommend that antipyretics be withheld in typhoid fever, without giving reasons for this advice.

Aspirin or an analogue is frequently given in typhoid for the fever, headache or other pain.

This study was undertaken in an attempt to ascertain the frequency and severity of this reaction.

Material

The case records of all patients with typhoid fever admitted to Groote Schuur Hospital from January 1952 to May 1955, inclusive, were studied. There were 43 cases. Of these, 8 had had aspirin or aspirin-containing drugs administered at some stage during their stay in hospital. In addition one case (Case 4) is included, admitted in 1949, which showed the reaction and to which my attention was drawn.

RESULTS

(*a*) *Patients to whom aspirin was administered and who showed the reaction*

There were 5 such cases, 2 of which (cases 1 and 2) I saw during the acutely-ill stage.

Case 1. B.D., a Coloured male aged 20 years, was admitted to the hospital on 6 May 1955, complaining of headache, malaise and feverishness which had been present for 4 days. On the day before admission he had been given 2 'APCs' by his private doctor and profuse sweating, weakness and collapse occurred shortly thereafter. On admission his temperature was 103°F, he looked ill and toxic, and his abdomen was distended. Chloramphenicol therapy was started after blood cultures had been taken. His condition remained unchanged for 3 days, and at 6.35 p.m. on 10 May 2 tablets of aspirin, phenacetin and codeine were given for his severe headache. This was followed by a rapid fall in temperature from 103°F, reaching a nadir of 95·6°F at 8.30 p.m. When seen at this stage the patient was very pale, collapsed and prostrated, with profuse sweating and bradycardia, and was gravely ill. The blood pressure had fallen from its previous level of 130/80 mm. Hg to 110/60 mm. Hg. A tablespoonful of sodium bicarbonate was given in an attempt to accelerate the elimination of the aspirin, and the pulse rate and temperature were recorded at half-hourly intervals until these had returned to their former level and the patient regained his former clinical state. This took approximately 7 hours. Subsequently the patient responded well to therapy and was discharged on 17 May. The temperature chart is reproduced in Fig. 1.

Case 2. J.R., a Coloured male, 22 years of age, was admitted to the hospital on 2 May 1955. He complained of headache, malaise and abdominal discomfort of gradual onset starting 3½ weeks before admission. On admission he was extremely ill and his temperature was 98·8°F. This had risen to 102°F by the following morning. At 9.30 p.m. on 3 May, two 5-gr. tablets of aspirin were administered for abdominal pain and headache. The patient lapsed rapidly into a state of profound asthenia and prostration, with sweating and bradycardia, and the temperature fell to 95·6°F within 2 hours. These symptoms subsided and the temperature returned to its former level after a total of 5½ hours.

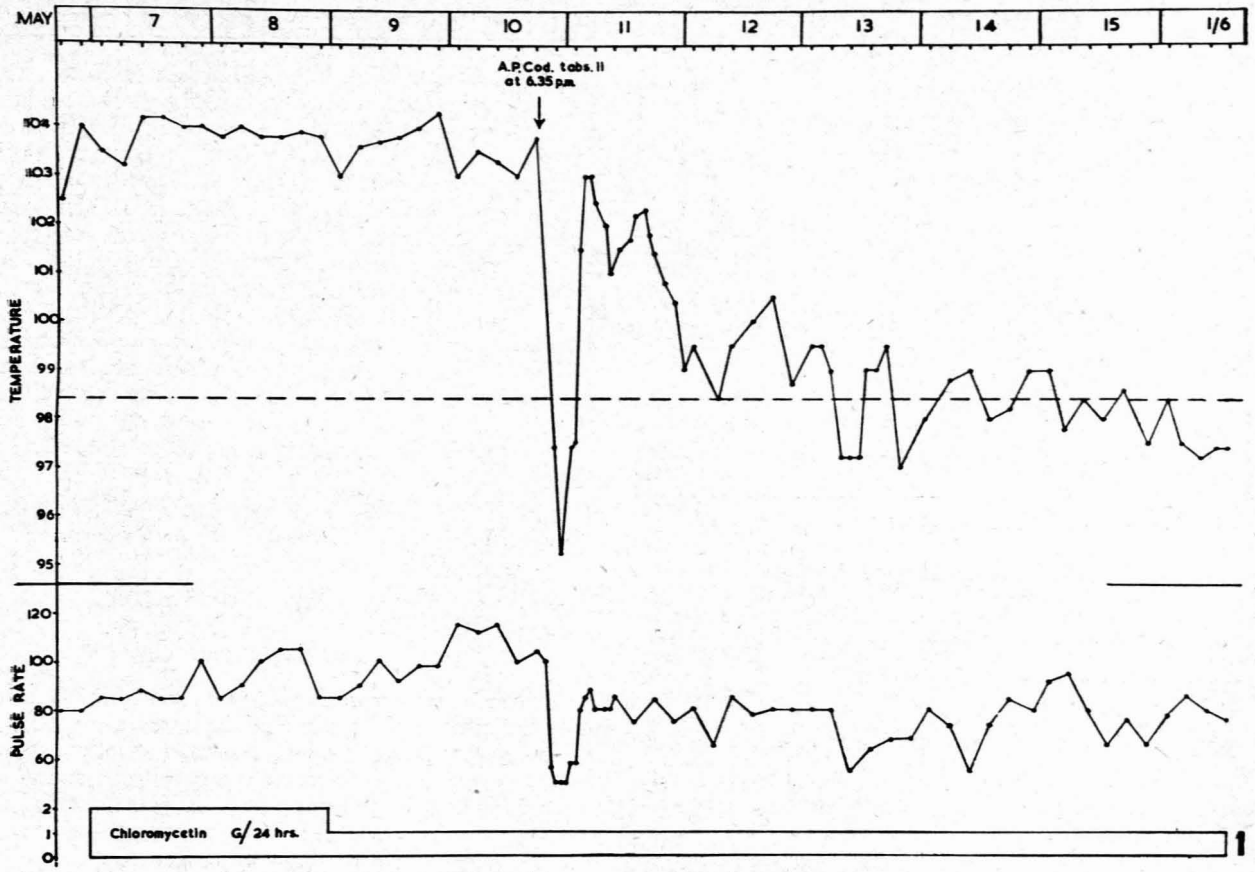

Fig. 1. Temperature chart of case 1.

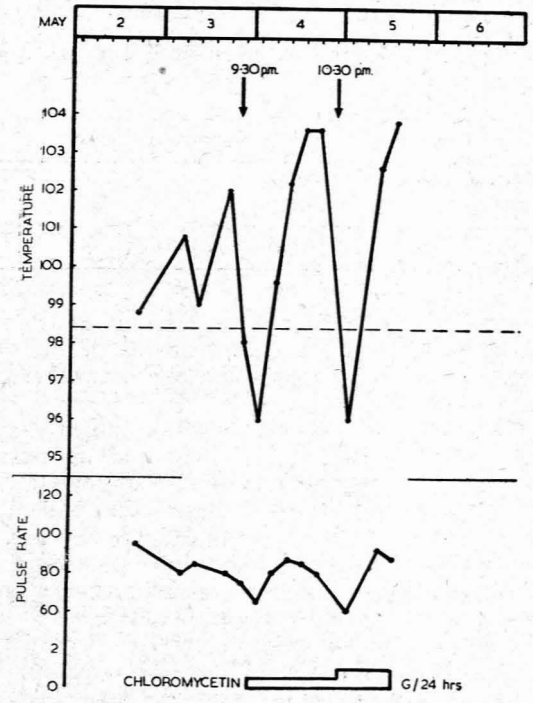

Fig. 2. Temperature chart of case 2.

On 4 May at 10.30 p.m. 2 tablets of aspirin were given with identical effect. He made an uneventful recovery on chloramphenicol. The temperature chart is reproduced in Fig. 2.

Case 3. K.L., a Coloured female of 21 years, was admitted on 16 April 1955 for investigation of symptoms of headache, feverishness and abdominal pain which had been present for 1 week before admission. When admitted she looked ill and apathetic and had a temperature of 102°F. A soft spleen was palpable. On 16 April 2 tablets of aspirin, phenacetin and codeine were given for the headache, with no apparent ill-effect and some relief of the headache. On 18 April, 15 gr. of aspirin were given at 6.35 p.m. This was followed by a sharp drop in temperature to 95°F, with sweating, collapse and bradycardia. After a total of 5½ hours she had regained her former state and made a subsequent complete recovery on chloramphenicol. The temperature chart is reproduced in Fig. 3.

Case 4. A.H., a White male of 29 years, was admitted on 2 July 1951, complaining of symptoms of headache, feverishness and general malaise for 5 days which had failed to respond to penicillin therapy. He appeared ill and toxic, with a high temperature and moderate splenomegaly. On 8 July 2 tablets of aspirin, phenacetin and codeine were administered and a sharp fall in temperature to 96°F followed. It was associated with a gravely collapsed state which caused considerable concern. After a total of 6 hours he had made a good clinical recovery from the acute episode, but his temperature took 12 hours to return to its previous level. The patient made a good recovery without specific antibiotic therapy. The temperature chart of this patient is reproduced in Fig. 4.

Case 5. J.S., a White female of 15 years, was admitted on 30 January 1952, on the 8th day of her illness. She was accompanied by a domestic temperature chart that had been kept by her mother, which showed an abrupt fall in temperature from

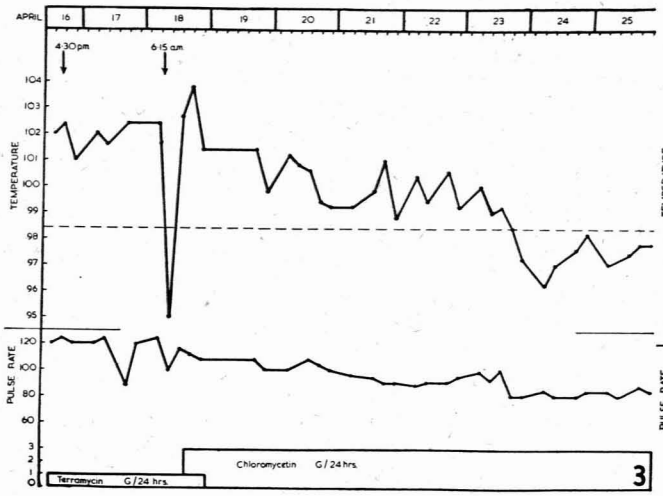

Fig. 3. Temperature chart of case 3.

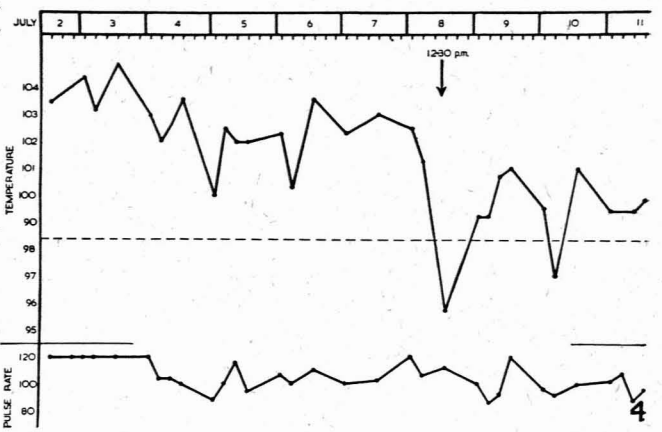

Fig. 4. Temperature chart of case 4.

106°F to 96°F following immediately upon the administration of 2 'gelonidas' on the day before admission. This, in the words of her private doctor in an accompanying letter, was associated with a 'grave deterioration in her clinical state'. She was treated with chloramphenicol, with defervescence on the 4th hospital day and subsequent complete recovery.

(*b*) *Patients to whom aspirin was administered without apparent ill effect*

There were 5 such cases, details of which are summarized in Table I. It will be seen that in 2 of these cases the drug was administered after defervescence had taken place.

(*c*) *Patients who showed sudden collapse with low temperature, where there was no good evidence of aspirin having been administered.*

There were 3 such cases. In 2 of them the collapse and hypothermia followed massive intestinal haemorrhage and responded well to whole-blood transfusion. In the 3rd case transient collapse with subnormal temperature was observed on the 2nd hospital day without any obvious cause being found. The ward sister, when questioned 4 weeks later, could remember aspirin having been given to the patient, but was uncertain of the precise time of administration of the drug.

(*d*) *Patients who did not receive aspirin and in whom there was no unexpected fall in temperature or deterioration in clinical state*

There were 31 cases in this remaining group.

DISCUSSION

The transient symptoms which followed shortly after the administration of aspirin in the cases quoted leave little doubt that patients with typhoid fever may respond to small doses of aspirin with prostration, sweating, bradycardia and hypothermia. It is evident that not all patients with the disease react in this way to aspirin, nor is it necessarily the invariable reaction of any one patient given aspirin on more than one occasion (e.g. case 3).

It is possible that a similar reaction might occur in other febrile diseases, but I could find no record of this. The literature on the subject of antipyretics in typhoid fever, though scanty, indicates that a similar reaction may be produced by other antipyretic drugs.

The mechanisms by which the effects of aspirin in the disease are mediated are obscure and permit of only the most tentative hypotheses. It is conceivable that one part at least of the reaction may be attributable to an increased vagus and parasympathetic action, for bradycardia is a prominent feature of the acutely-ill phase and the general clinical state bears a certain

TABLE I. CASES IN WHICH ASPIRIN OR ASPIRIN-CONTAINING DRUGS WAS GIVEN WITHOUT APPARENT ILL-EFFECTS

Case	*Age*	*Race*	*Sex*	*Drug and dose*	*When given (before or after defervescence)*	*Other therapy at time aspirin was given*
6	21	C	F	'Disprin' 10 gr.	After	Chloramphenicol, 3 g. per day
7	42	C	M	A.P. Cod., 2 tabs.	Before	None
8	39	C	M	A.P. Cod., 2 tabs.	Before	Penicillin and streptomycin
9	35	C	M	Aspirin, 30 gr. per day for 1 week	Before	None
10	22	C	F	Aspirin 10 gr.	After	Chloramphenicol

resemblance to that seen in the so-called 'vaso-vagal' attack.

Dr. Rachel Rabkin (1955) has suggested that the reaction is more likely to occur when the drug is administered to fasting patients, but there was nothing in this series to confirm or refute this suggestion.

A sudden fall in temperature with clinical deterioration during the course of typhoid fever is seen chiefly in association with the complication of haemorrhage or intestinal perforation, and awareness of the occurrence of this reaction following aspirin should obviate a mistaken diagnosis of one of these complications. As the administration of aspirin is not usually placed under the direct supervision of the medical staff, ward sisters should be warned of the dangers of giving aspirin to cases where typhoid fever is suspected.

The effects in all the cases in this series were transient and did not appear to influence the ultimate recovery.

The treatment of the patient during the acute phase of the drug-induced illness does not present a very great problem, since recovery may be expected after a matter of hours. One might expect sodium bicarbonate, through its action in hastening the elimination of aspirin, to be effective, but no convincing effect was seen when it was used in case 1.

SUMMARY

A series of 44 cases of typhoid fever is presented, 5 of whom illustrated a reaction that may follow the administration of aspirin to patients with this disease. This reaction, characterized by collapse, sweating, bradycardia and hypothermia, occurs shortly after the taking of the drug and subsides within a matter of hours.

Case histories are given.

My thanks are due to Dr. N. H. G. Cloete, Medical Superintendent of Groote Schuur Hospital, and to Professor J. F. Brock, Head of the Department of Medicine, for permission to publish these cases. In addition, I acknowledge, with gratitude, the generous advice and assistance of Dr. C. Merskey in the preparation of this paper.

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