Discussion

Although there is a good deal of strain variation in sensitivity, the results afford a fairly clear picture. Three of the four species are fully sensitive to penicillin: this accords with the majority of published results for *Bacteroides necrophorus*, and is in accordance with expectation for *Bacteroides fusiformis* in view of the therapeutic action of penicillin in Vincent's infection. *Bacteroides melaninogenicum* is very highly sensitive: to know this may be of importance in connexion with a form of subcutaneous gangrene spreading from an abdominal operation wound and accompanied by a foul-smelling dark brown discharge, in two cases of which I have found this organism. On the other hand, *Bacteroides fragilis* is much more resistant, and authors who have reported such resistance in unidentified *Bacteroides* organisms may have been dealing with this species. Since this species is so closely associated with the lower bowel, it might be a sound policy to assume that most *Bacteroides* infections arising in this area will be penicillin-resistant.

Streptomycin clearly has no place in treating any of these infections. Oxytetracycline is consistently more active than chloramphenicol, and it is likely that other tetracyclines will behave similarly: chlortetracycline has been used successfully by several authors already quoted. The superiority of oxytetracycline over any other antibiotic in activity against *Bacteroides fragilis* is interesting in view of the remarkable efficacy of this antibiotic in treating peritonitis due to a perforated viscus, although in this connexion action on other bacteria must also be important. Veillon and Zuber (1898) found this organism constantly present in the pus of appendicitis, and although they are rarely identified, such organisms are frequently numerous in the peritoneal exudate due to perforation of any part of the lower bowel.

Of the remaining antibiotics tested, erythromycin is highly active only against *Bacteroides melaninogenicum*, and this is the only species against which bacitracin has any action at all in the concentrations used. Polymyxin is uniformly active against all species except *Bacteroides fragilis*. It seems unlikely that the use of any of these three antibiotics could be specially indicated for these infections.

The mere existence of a *Bacteroides* infection can often be demonstrated or confidently deduced within a short time, but to isolate and identify the organism and test its sensitivity to antibiotics will take at least a week, although some useful information may be obtained by a sensitivity test (cup or disk method) in primary culture. It is thus desirable to have some general policy for the immediate treatment of these infections. The policy suggested by these results is that one of the tetracyclines should be used for infections originating in the lower bowel, and penicillin for all others, unless they are mixed, when the choice will depend partly on the sensitivities of the other bacteria.

Summary

Existing information about the sensitivity of different species of *Bacteroides* to antibiotics is incomplete and contradictory.

Bacteroides fusiformis (6 strains), *necrophorus* (4), *fragilis* (23), and *melaninogenicum* (22) have been tested for sensitivity to seven antibiotics by a falling dilution method over a full range of therapeutically attainable concentrations.

Penicillin equals or exceeds other antibiotics in activity against three of these species: *Bacteroides fragilis* is resistant to penicillin, and most sensitive to oxytetracycline. All species are relatively resistant to streptomycin and moderately sensitive to chloramphenicol.

A therapeutic policy for these infections is proposed, to be applied in the absence or in advance of laboratory data.

Almost all the difficult and laborious work of isolating and maintaining these strains, as well as the sensitivity testing, was

carried out by Miss Pamela M. Waterworth, to whom I express my grateful thanks.

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ASPIRIN AND GASTRIC HAEMORRHAGE

BY

A. P. WATERSON, M.D., M.R.C.P.

Demonstrator in Pathology, University of Cambridge

Since the observations of Douthwaite and Lintott (1938) there has been no doubt that aspirin can cause gastric haemorrhage, but most of the information on this topic has been in the form of reports of one case or of a small number of cases—for example, Hurst and Lintott (1939), Crismer (1947), Dumont-Ruyters (1948), Richmond (1950). There had been little published on its general frequency as a cause of haematemesis or melaena serious enough to cause admission to hospital until Muir and Cossar's (1955) observations that about one-third of patients with peptic ulcer, and about one in twenty of a series of control patients, complained of dyspepsia after taking this drug. They suggested that in one in eight cases of haematemesis aspirin had been "at least a contributory cause" of the bleeding.

In every series of cases of haematemesis and melaena there are some which defy diagnosis in spite of every investigation, including exploratory laparotomy and even post-mortem examination. Probably, as Tidy (1950) says, Hurst (1943) overstated the case when he alleged that about half the "undiagnosed" cases might be found to be due to aspirin. Avery Jones (1952) confessed to "a strong clinical impression" that an occasional case is due to aspirin idiosyncrasy. In the course of a recent survey of a series of cases of gastric and duodenal haemorrhage patients were asked about their "aspirin habits."

The object of this inquiry was threefold: (1) To find out the "aspirin habits" of the patients concerned, especially their reasons for taking the drug, their method of taking it, and whether it usually caused any symptoms. (2) To discover whether any cases might reasonably be attributed to the drug alone—that is, in patients with no evidence of any other possible cause of the bleeding. (3) To investigate the circumstances of any such cases, and, by comparison with reported cases, to find any common features which led to the administration of the aspirin, with a view to preventing a recurrence.

The patients were asked about their habits, and whether they had observed any untoward effects. A few have been omitted, mainly those who were too ill to be interrogated or those who were mentally incapable of giving a coherent answer or even of understanding the question. Of the former, it is almost certain that none were cases of aspirin haemorrhage, the lesion

responsible having been established by radiography, operation, or post-mortem examination.

Results of the Inquiry

Habits of Aspirin-taking.—The 170 admissions in the series involved 165 patients. The "aspirin history" was obtained in 151 of these, of whom 34 never took aspirin in any form. Of the remaining 117, 106 were diagnosed as having "proved or probable peptic ulcer." The 117 patients yielded the following data:

Reasons for Taking Aspirin.—About one-third of the patients gave more than one reason. The reasons are analysed as follows: headache (including one case of migraine), 52; for sleeping, 29; colds and "flu" (including two prophylactically), 26; for pain (arthritis, phantom limb, etc.), 17; abdominal pain, 17; as a "tonic," 13; "because my wife takes them," 3; hangover, dental extractions, dysmenorrhoea, menopausal flushes, and feverishness, 1 each.

Method of Taking Aspirin.—This information is available in 115 of the 117 patients: swallowed whole, with a minimum of water, 67; swallowed whole, with a good drink, 25; swallowed whole, with no water, 5; crushed, with a minimum of water, 8; crushed, with a good drink, 10.

Unwanted Effects.—28 patients complained of symptoms after taking aspirin: Dyspepsia, nausea, vomiting, or heartburn, 24; palpitation, 3; swelling of lips, 1; "suffocation" and salivation, 1. The patient complaining of "suffocation" and salivation was one of the 24 who complained of dyspepsia.

There was no correlation between the method of taking the drug and the occurrence of these effects, although one patient found that the taking of water with the tablets definitely lessened the dyspepsia which usually occurred afterwards.

Cases of Aspirin Haemorrhage.—In 3 of the 170 cases under investigation there was reasonably good evidence that aspirin could be incriminated as the cause of the haemorrhage. The circumstances in which this had occurred are reviewed in connexion with the other reported cases below.

Circumstances of Aspirin Haemorrhage

The cases fall into three fairly definite groups: (1) Those in which the aspirin was taken for some painful illness entirely independent of the gastro-intestinal tract. (2) Those in which the aspirin was taken because of abdominal pain. (3) The unwitting treatment of a sensitive patient in hospital.

Group 1

Many of these patients complain of low back pain or "sciatica." Some have one or other kind of chronic arthritis, but various acute or chronic painful disorders have been responsible—for example, migraine in Hurst and Lintott's case, and renal colic in Richmond's case. It is the presence of this separate disease which may give the clue to the possibility that aspirin may have been the provocative cause of the bleeding. The following two cases fall into this category.

Case 1.—A farmer's wife aged 56 was admitted to hospital on August 29, 1951. Twelve days before admission she had retired to bed with "lumbago and sciatica." For about a week before admission she had complained of intermittent gnawing abdominal pain. Three days before admission she fainted and immediately afterwards vomited not more than a pint (570 ml.) of dark red blood. She had black stools in the next three days. During the few days before the haematemesis she had been taking 10 gr. (650 mg.) of aspirin when necessary, and 5 gr. (320 mg.) of aspirin in a compound tablet at night. She knew that aspirin usually caused nausea or actual vomiting, and had always avoided it in the past. An hour before the haematemesis, after breakfast, she had taken 5 gr. (320 mg.) of aspirin, crushed in milk; this was followed by epigastric discomfort. On admission she was observed to be an obese woman, with a pulse rate of 100 and blood pressure 190/100. Apart from slight epigastric tenderness there were no other abnormal findings. She made an uneventful recovery without transfusion, and had no more abdominal pain after admission. An x-ray examination 12 days after admission showed no abnormality.

Case 2.—A publican's wife aged 65 was admitted to hospital on May 4, 1952, complaining of low back pain, radiating down the left leg, of seven days' duration. She had been in bed for

four days. She had been in the habit of taking two tablets each containing $7\frac{1}{2}$ gr. (500 mg.) of aspirin at bedtime if she had a headache; the last occasion was two weeks before admission. This sometimes gave her mild heartburn. In the four days before admission she had been taking codeine compound tablets (N.F.), each tablet containing 4 gr. (250 mg.) of aspirin, for the sciatic pain, one four-hourly and two at night, swallowed whole with a minimum of water. The first night she took them (May 1) she woke up feeling ill, with retrosternal pain. She had taken two doses on the day before admission. She was about to take a third dose, when she felt faint and vomited about a pint (570 ml.) of dark red blood. She then passed a loose stool of normal colour. On admission she was found to have a pulse rate of 94 and a blood pressure of 160/115. She was an obese woman with no abdominal tenderness. She made an uneventful recovery without transfusion. X-ray examination eleven days after admission, and again seven weeks after admission, showed no abnormality.

Group 2

Abdominal pain is often treated by the patient himself, not only with proprietary preparations of alkalis, but also sometimes with large doses of aspirin. Of the 117 patients in the series whose aspirin habits are known, 17 admitted that they took it for abdominal pain, 5 of them frequently or regularly, all with some relief of pain. One (Case 3) had taken about 600 gr. (39 g.) of aspirin in three weeks for abdominal pain.

Case 3.—A railwayman's wife aged 58 was admitted to hospital on June 16, 1952. For two months she had had pain in the left hypochondrium, with flatulence. Three weeks before admission she had a transient dizziness when passing a stool. She had been pale, and had a poor appetite, for about three or four weeks. She had been taking aspirin at the rate of approximately 40 5-gr. (320-mg.) tablets a week, swallowed whole with a good draught of water or other fluid. During the three weeks before admission she had taken approximately 600 gr. (39 g.) of aspirin. This relieved the epigastric pain at first, but soon began to give her "a burning feeling between the breasts" each time she took it. At this time, too, she began to feel dizzy on occasion while out shopping. Three days before admission she felt faint all day. The day before admission she felt worse, and stayed in bed all day; she vomited several times, at first brown fluid and later bright red blood, and was admitted to hospital early the next morning. On admission she was found to be a very ill, shocked woman, with a pulse rate of 120. Her blood pressure was not recordable. She was given a blood transfusion of 4 pints (2.3 litres), and made an uneventful recovery. X-ray examination seven weeks after admission showed no abnormality.

Group 3

In hospital, medicines are rarely refused, and a patient who scrupulously avoids all aspirin preparations may not think it worth mentioning this when offered tablets crushed in a spoon. It is possible that some haematemeses occurring in hospital and otherwise unexplained may in fact have been provoked by aspirin. The following case is that of a patient whose haematemesis was probably caused by aspirin.

Case 4.—A woman aged 49 was admitted to hospital as an emergency on January 13, 1951, with a history of flatulent dyspepsia, especially after fatty foods, for many years. Three years previously she had an attack of colicky abdominal pain lasting 24 hours, during which she fainted and after which she was jaundiced for a week. The dyspepsia and flatulence had grown steadily worse during the past three years. On the day of admission she woke with a slight epigastric pain, which grew worse during the day and became colicky. She vomited once and passed six fluid stools. She was in severe pain on admission, but not jaundiced. There was tenderness over the upper abdomen, especially under the right costal margin. There were no other abnormal findings. On January 15 the haemoglobin was 14 g. per 100 ml., and so it is unlikely that the loose stools two days before admission contained any appreciable quantity of blood. The pain was relieved by morphine and pethidine, but she still had some pain in hospital. On January 19 she had three haematemeses of dark blood with clots, a total loss of approximately 2 pints (1,140 ml.), for which a transfusion was given. X-ray examination 41 days after admission revealed a "slight deformity" of the duodenal cap. A cholecystogram was normal.

The patient was readmitted again in April, this time jaundiced, and again in July, when a laparotomy was done. The stomach and duodenum was found to be normal; there were some adhesions around the gall-bladder, and some "biliary mud" was

evacuated, but no true calculi were found. She was well when last seen as an out-patient on November 22, 1951.

During her first admission to hospital she was given 2 codeine compound tablets (*N.F.*) crushed, with a little water, on three successive days after admission, without knowing that she was being given aspirin. In the past all aspirin preparations, including codeine compound tablets and also the "soluble" brands of the drug, had made her sick within a few hours, even when taken crushed and with a cupful of water. She vomited several times in the first few days in hospital, but not after the haematemesis.

In view of the equivocal findings of the opaque meal, it is suggested that there is strong presumptive evidence that the bleeding in this case was caused by the administration of aspirin.

Discussion

These observations were made in the course of a survey of the underlying lesions of gastric and duodenal haemorrhage. This was not primarily concerned with the role of aspirin in causing exacerbations of symptoms, or haemorrhage, in patients with peptic ulcer. Muir and Cossar (1955) show that patients with peptic ulcer have a much higher incidence of intolerance to aspirin than the rest of the population, and this is confirmed. Some of the undiagnosed cases in the "acute lesion group" had taken aspirin in the 24 hours before admission, but only those cases are reported in which the connexion appears to be unequivocal.

Aspirin is so valuable a drug, and so ubiquitously used, that any toxic effects are likely to have an economic significance, as well as causing distress to patients individually. Gastric haemorrhage is undoubtedly one of the most serious of its toxic effects, and an inquiry should always be made about it in any case of gastro-intestinal bleeding, because it is so frequently self-administered and so easily obtained. The doses taken may be massive—for example, Neale (1936) has recorded a case in which the patient took 200 gr. (13 g.) in 36 hours, for the pain of a tuberculous hip-joint.

However, only a small number of people have an intolerance to the drug serious enough to warrant complete abstinence from it in any form. Various preparations have been tried, many of which are far less apt to cause trouble than the simple compound. These include calcium aspirin (Thompson and Dragstedt, 1933), buffered aspirin (Tebrock, 1951), and enteric-coated aspirin (Talkov *et al.*, 1950). Finally, there are a few people who are liable to develop really serious allergic reactions with aspirin, and they should be careful, especially when under medical care, to avoid it—no easy task when so many tablets and mixtures contain it. Such people are rare, and it would be a pity if the advantages of so valuable an analgesic were to be denied unnecessarily to those who would benefit from it.

Summary

Of 165 patients admitted to hospital with haematemesis and melaena 151 were studied with regard to the taking of aspirin; 34 never took aspirin; of the other 117, 28 complained of some undesirable side-effects, of which 24 were epigastric pain, nausea, vomiting, or heartburn. There was no correlation between the method of taking it and the occurrence of these symptoms. Among 170 episodes of haematemesis or melaena there were three which gave reasonably good evidence for supposing that the aspirin had caused the bleeding, in the absence of any other gastric lesion.

These three cases, together with a fourth case not in the series of 170, and others from the literature, are analysed. The analysis shows that this bleeding occurs in one of three circumstances: (1) aspirin taken for some painful disorder independent of the gastro-intestinal tract; (2) self-medication for abdominal pain; or (3) the unwitting treatment of a sensitive patient in hospital.

As serious intolerance occurs in only a small number of patients, and as aspirin is so valuable an analgesic, patients should not be forbidden it unless this is really

necessary, but, if they are, they should be warned to be suspicious of any analgesic offered to them, for many of these contain aspirin. Those who have minor gastro-intestinal symptoms from the drug should take a preparation such as calcium aspirin or enteric-coated tablets if these are available.

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COMBINED ANTIHAEMOPHILIC GLOBULIN AND CHRISTMAS FACTOR DEFICIENCY IN HAEMOPHILIA

BY

MARC VERSTRAETE, M.D.*
Assistant, Department of Medicine

AND

J. VANDENBROUCKE, M.D.
Professor of Medicine

From the Physiopathology Laboratory, University of
Louvain, Belgium

In the last year haemophilia has been separated into different types—namely, the well-defined classical haemophilia A (antihaemophilic globulin deficiency) and Christmas disease or haemophilia B (Christmas factor deficiency, factor IX deficiency, plasma thromboplastin component deficiency). Another haemorrhagic diathesis resembling haemophilia but apparently dominant in character has been described as plasma thromboplastin antecedent deficiency (P.T.A. deficiency or haemophilia C).

Since the different types of haemophilia have been discovered only one case of mixed haemophilia has been described (Soulier and Larrieu, 1953). This condition is extremely rare.

The patient described in this paper is one of 43 patients clinically thought to have haemophilia, of which 4 had haemophilia B and 39 had haemophilia A. Our purpose is to study the haemorrhagic diathesis occurring in one family in which five males of the last generation were affected. Two of them bled to death in childhood. The remaining three were fully investigated. The point of particular interest in this family is that the type of haemophilia is not the same in all the affected members.

Methods

Platelets were counted by the method of Van Goidsenhoven (1926). The clotting-time was determined by the Lee and White (1913) method, the bleeding-time

*Presently Research Fellow, Vascular Research Laboratory, Cornell University Medical College, New York, N.Y.