IMPORTANCE OF ASPIRIN AS A CAUSE OF ANAEMIA AND PEPTIC ULCER IN RHEUMATOID ARTHRITIS

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Few would question the value of aspirin (acetylsalicylic acid) in the treatment of rheumatoid arthritis. Carefully controlled trials (Empire Rheumatism Council, 1957; Medical Research Council and Nuffield Foundation, 1957) have shown little difference between the therapeutic effect of aspirin and cortisone in the long-term management of this disease.

A number of reports have been published which suggest that aspirin may be an important cause of gastro-intestinal bleeding. Douthwaite and Lintott (1938) reported that aspirin can cause anaemia, and showed by gastroscopy that it had an irritant action on the gastric mucosa. Their conclusions were questioned by Paul (1943), who observed no aspirin effect in 1,000 gastroscopies. In a further study of the effects of aspirin, Douthwaite (1954), using a slightly different method, found a positive flare reaction in 17 out of 37 patients taking ordinary aspirin but no gastric irritation in 12 patients taking soluble aspirin.

Muir and Cossar (1955) studied the effect of aspirin in patients with peptic ulcer. They found that administration of aspirin to patients with radiological evidence of peptic ulcer was followed by increased gastric secretion and the appearance of occult blood in the stools. A study of gastrectomy specimens from patients who had been given aspirin shortly before operation showed mucosal irritation in 12 out of 20 given aspirin but in only 2 out of 20 given calcium aspirin. They found the incidence of dyspepsia in 300 controls taking aspirin to be 5% compared with 33% in 318 patients known to have peptic ulcers. Of 83 such patients having frequent exacerbations of symptoms 33 had taken aspirin within 24 hours, and 8 of these blamed aspirin for their symptoms. They also found 15 patients with chronic dyspepsia which subsided when aspirin was withdrawn. A further analysis of the histories of 166 patients admitted with haematemesis revealed that 30% had taken aspirin within six hours of the haemorrhage. In a group of patients with acute haemorrhages but without previous symptoms, this rose to 50%. Among patients entering hospital for other reasons only 5% had consumed aspirin within six hours of admission. Muir and Cossar (1959) again found that 57 out of 106 patients admitted with gastro-duodenal haemorrhage had taken aspirin within 48 hours of their initial bleed, compared with 17% in a group of 106 admitted for other reasons.

Kelly (1956) reviewed the literature and reported three cases with repeated gastro-intestinal haemorrhage related to aspirin consumption which did not recur when aspirin was avoided. Schneider (1957) found that ordinary aspirin led to the appearance of occult blood in gastric secretions, while calcium aspirin did not. Lange (1957) reported persistent occult blood in the stools of patients

taking aspirin, though it occurred less often with coated aspirin and when the tablets were taken with meals. He also found that 45% of 96 patients with gastro-intestinal haemorrhage had taken salicylates prior to admission. Alvarez and Summerskill (1958) considered that the taking of salicylates was a precipitating factor in 40% of 103 patients admitted for massive gastro-intestinal bleeding. They found that the incidence of radiologically proved ulcers in this group was low, suggesting that haemorrhage had occurred from acute lesions. They demonstrated occult blood in the stools of 50% of healthy individuals, patients with peptic ulcers, and patients with dyspepsia who had taken either soluble or insoluble aspirin by mouth. They found no evidence that soluble aspirin reduced the risk of major bleeding, and no relationship between the method of taking salicylate preparations and the occurrence of haematemesis and melaena. In a further paper (Summerskill and Alvarez, 1958) they reported two cases of severe anaemia in patients who had taken large amounts of salicylates. After a substantial reduction in dose there was no recurrence of anaemia for periods of 7 and 10 months.

Stubbé (1958) found that 70% of 140 patients admitted with rheumatic complaints and also 70% of 40 healthy controls who took aspirin had occult blood in their stools. Bleeding was unrelated to dyspepsia, dose, or mode of administration of the drug. Porter, Lewis, and Dixon (1959), using red cells tagged with ^{51}Cr , estimated a loss of blood which was usually less than 5 ml. daily in all 11 subjects taking either aspirin or calcium aspirin. This loss was diminished or absent when enteric-coated aspirin was substituted.

On the basis of this evidence it has been suggested that aspirin is a potentially harmful drug, and extravagant claims have been made on behalf of a number of other analgesics whose value in the treatment of rheumatoid arthritis has never been assessed by controlled trials and whose potential side-effects during long-term administration are not yet clearly known. The evidence that aspirin causes bleeding from the gut must be accepted, but it is entirely possible that many other drugs not yet tested may have a similar effect. In any case, such chronic loss of blood is only of importance if it is of a magnitude sufficient to decrease iron stores to an extent likely to cause anaemia.

In view of the possibility that the reputation of an exceedingly useful drug might suffer unnecessarily, it was decided to study the variations in haemoglobin levels in a large group of patients with rheumatoid arthritis, most of whom had been taking aspirin continuously or intermittently in varying doses for a number of years.

Materials and Methods

The case records of 244 patients suffering from rheumatoid arthritis admitted between June, 1948, and July, 1951, to the rheumatism unit of the Northern General Hospital, Edinburgh, were studied. The composition of the group is shown in Table I. The progress of this group since discharge from the hospital has already been reported in detail by Duthie, Brown, Knox, and Thompson (1957). Haemoglobin levels were measured colorimetrically by the alkali-haematin method of Clegg and King (1942), with 100% haemoglobin equal to 14.8 g./100 ml. The mean levels of haemoglobin for the whole group on admission, at discharge, and at approximately two, four, and six years thereafter were

TABLE I.—*Composition of the Group*

Data	Males	Females	Total
No. of cases of rheumatoid arthritis admitted between June, 1948, and July, 1951			307
Period between discharge and final assessment (months)	67.4 (range 52 to 92 months)		
No. of deaths between discharge and final assessment	14	22	36
No. no longer available			27
„ available at final assessment	62	182	244
Mean age at third assessment	54.1	55.3	
Mean duration of disease at third assessment (6 years)	11.3	12.5	

determined. A more detailed study was made of those patients in whom the haemoglobin level had varied by more than 20% during the period under review. Detailed information was sought about the incidence of dyspepsia and peptic ulceration.

Results

Table II shows the mean haemoglobin levels of the whole group on admission, at discharge, and at approximately two, four, and six years thereafter. The great

TABLE II.—*Changes in Mean Haemoglobin Levels Between Admission and Third Assessment*

	Whole Group (244)	Adequate Salicylates (75)	Nil or Occasional Salicylates (31)
Admission	82.7 ± 17.68	83.0	87.2
Discharge	86.7	85.0	90.9
First assessment	82.4	82.0	86.4
Second „	79.6	79.6	82.8
Third „	92.4 ± 10.84	92.1	97.4

majority of the patients were on regular aspirin, but in many cases the exact dosage was not known. To overcome this possible bias 75 patients known to have taken regularly at least 40 gr. (2.6 g.) and usually 60 gr. (3.9 g.) of aspirin daily were compared with 31 patients known to have taken none or only very occasional doses of salicylates. It can be seen that there has been an overall gain in the mean haemoglobin level of the group after six years, and also that the group on adequate salicylates throughout this time showed a similar increase in mean haemoglobin level to that of the group on none or only very occasional doses of the drug.

TABLE III.—*Variations in Haemoglobin Levels Between Admission and Third Assessment in 244 Cases*

Final haemoglobin within 20% of admission level	185 (75.8%)
Rose 20%	55 (22.6%)
Fell 20%	4 (1.6%)

Table III shows the variations in the haemoglobin level of the whole group: 75.8% remained at or about the same level; in 22.6% the mean haemoglobin rose more than 20%; and only four patients (1.6%) showed a drop of over 20%.

TABLE IV.—*Incidence of Dyspepsia in 244 Cases*

Dyspepsia noted	30 (12.3%)
Peptic ulcers (before admission, 7; after admission, 3)	10 (4.1%)
Other causes (ulcerative colitis, 2; chronic cholecystitis, 2; hiatus hernia, 2)	6 (2.5%)
No cause found	14 (5.7%)

Table IV shows that 30 patients (12.3%) complained of dyspepsia, troublesome enough to be noted on the case sheet. In only 10 patients (4%) was there clinical or radiological evidence of peptic ulcer. Six other patients had gastro-intestinal lesions which could contribute to dyspepsia, leaving 14 subjects (6%) with unexplained dyspepsia.

At the final assessment the haemoglobin was below 80% in 27 patients (11%). In only three of these was there evidence of peptic ulcer. Other diseases that might have a bearing on the anaemia were present in 12 instances, but in the majority the cause was undoubtedly rheumatoid arthritis in an active phase.

Discussion

Reports have appeared in the literature of the persistence of occult blood in the stools of patients taking salicylates, but from the results of the present study it is clear that it is of little importance as a cause of anaemia in patients with rheumatoid arthritis who have taken the drug over a period of years.

Further evidence against the idea that salicylates are an important cause of anaemia is provided by comparing the progress of a small group of patients who were not taking regular aspirin with another small group who were taking regular and adequate doses of the drug. The group not requiring aspirin (Table II) started with a higher haemoglobin level and gained in about the same proportion as the group on regular doses. These two groups, though probably differing in the activity of their disease, showed an equal gain after six years, providing further evidence of the unimportance of the minimal blood loss due to aspirin.

Table III shows the variations in haemoglobin levels throughout the period of study: 75.8% of the subjects remained at or about the same level; and 22.6% had an increase of over 20% in their haemoglobin level. In 65% of those whose haemoglobin rose oral or parenteral iron was known to have been given. Only four patients (1.6%) showed a fall of over 20%. Of these, one had a definite ulcer, one was found to have pernicious anaemia, and in one the disease was very active. The fourth patient had a low haemoglobin level recorded on one occasion which subsequently returned to normal.

Analysis of the whole group (Table IV) showed that 30 patients (12.3%) had suffered from dyspepsia. This compares with an incidence of 5% in 300 people representing an average cross-section of the community reported by Muir and Cossar (1955). Included in this group of 30 dyspeptics were 10 patients (4%) with clinical or radiological evidence of peptic ulcer. Only three (1.2%) developed their ulcer during the period of observation. Six of the remaining dyspeptics had other causes for their symptoms, but there were 14 patients (6%) in whom a definite diagnosis of ulcer could not be made. The incidence of definite ulcer in this series is a little under 5%, and if it is presumed that all 14 cases of unexplained dyspepsia had ulcers as well, this would mean an incidence of about 10%. Other estimates of the incidence of peptic ulcer in the general population vary from 5% to 15% with most authors, suggesting an overall incidence of around 10% (Harrison, 1950; Ivy, Grossman, and Bachrach, 1950; Doll and Jones, 1951; Sandweiss, 1951). A previous study on patients with rheumatoid arthritis (Short, Bauer, and Reynolds, 1957) revealed a frequency of 5.6% in 650 patients with rheumatoid arthritis. It would thus appear that, even if the majority of patients with unexplained dyspepsia are accepted as also having ulcers, there is no good evidence that aspirin causes an increased incidence of peptic ulcer in patients with rheumatoid arthritis.

In the analysis of patients with a final haemoglobin level below 80% a number of factors might have

contributed to the low level, but in only three of this group was there any suspicion of ulcer, and in only one was this confirmed radiologically. Nine patients were severely debilitated, and the low haemoglobin in the other six may have been related to disease activity, though a silent ulcer or gastro-intestinal haemorrhage cannot be excluded.

Conclusion

A study of 244 patients with rheumatoid arthritis followed for about six years has been made with particular reference to their intake of salicylates, haemoglobin levels, and the incidence of dyspepsia or ulcer. The great majority were on regular doses of aspirin.

Over the six-year period the group showed a significant increase in haemoglobin level. A smaller group not on regular aspirin showed a comparable increase.

Only three patients (1.2%) were known to have developed clinical or radiological evidence of peptic ulcer while on aspirin. Seven other patients had or were suspected of having an ulcer before they developed rheumatoid arthritis.

The incidence of peptic ulcer in this series compares favourably with that in the general population.

It is concluded that the great majority of patients with rheumatoid arthritis can tolerate regular aspirin without an increase in anaemia. The dangers of causing peptic ulceration or precipitating gastro-intestinal haemorrhage appear to have been greatly exaggerated.

During the period when this work was done, one of us (F.D.B.) was supported by a Research Fellowship from the Canadian Arthritis and Rheumatism Society, and the Rheumatic Diseases Unit was in receipt of grants from the Nuffield Foundation, Medical Research Council, and Boots Pure Drug Company Limited.

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FULMINATING AND FATAL PNEUMONIA AND SEPTICAEMIA DUE TO ACHROMOBACTER ANITRATUS

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Achromobacter anitratus was first described by Schaub and Hauber in 1948. Since then several authors have isolated this organism from patients with various illnesses, but without convincing proof of its pathogenicity. The following report gives evidence that the organism may be highly pathogenic.

Case History

A man aged 50 had had chronic bronchitis for ten years. In 1956 he had lobar pneumonia and recovered slowly but satisfactorily. He remained well until October 24, 1957, when he felt abnormally tired but noticed nothing else. At 2 a.m. on October 25 he was awakened by a rigor; he felt progressively feverish and unwell and began to cough up pink froth. He complained of pleuritic pain over the anterior and upper part of the left side of the chest. His condition gradually deteriorated, and when seen by his family doctor at 1 p.m. the same day he was cyanosed and orthopnoeic; his temperature was 100° F. (37.8° C.) and the pulse very weak.

He was admitted to hospital at 5 o'clock the same evening and was obviously very ill, distressed, and confused, with central cyanosis and marked tachypnoea. The pulse volume was poor, the rate 100, and the blood-pressure 110 mm. Hg systolic and 70 mm. diastolic. The percussion note was impaired over the left upper lobe anteriorly and there was bronchial breathing with medium crepitations in the same area. Medium crepitations were also heard over both lower lobes. The white cell count was 13,200/c.mm. (77% polymorphonuclear neutrophils, 3% eosinophils, 5% monocytes, and 15% lymphocytes), and the haemoglobin 98% (14 g./100 ml.). A diagnosis of fulminating lobar pneumonia was made. The probable pathogenic organism was thought to be *Staphylococcus aureus*, which had often been found in similar cases at this time during the epidemic of Asian influenza. Penicillin 250,000 units and streptomycin 0.25 g. were given intravenously at once, and 3 million units of penicillin with 0.5 g. of streptomycin intramuscularly and repeated every two to three hours.

An hour after admission the patient's condition had further deteriorated, and both the cyanosis and the dyspnoea had greatly increased. The systolic blood-pressure had fallen to 90 mm. Hg, the diastolic being unrecordable. An intravenous drip of glucose-saline was set up, and by this means 5 mg. of noradrenaline was rapidly given. Hydrocortisone 100 mg. was also given intravenously, and erythromycin 1 g. by mouth. The blood-pressure returned to 110/70 mm. Hg for a few minutes, but it quickly sank again to unrecordable levels although a total of 20 mg. of noradrenaline was given during the next six hours. His condition continued to deteriorate rapidly; he became comatose, and at 2.15 o'clock the next morning he died, 24 hours after the initial symptoms.