Summary

Urinary H.C.G. assays have been performed in 90 patients with hyperemesis gravidarum and the results have been compared with those in a series of 20 normally pregnant women. The hyperemesis patients were observed in Aberdeen and in Newcastle upon Tyne and the normal subjects in Newcastle upon Tyne and in Edinburgh.

The mean H.C.G. excretion from the seventh week of pregnancy onwards in the hyperemesis patients from Aberdeen did not differ significantly from the corresponding value in the Newcastle upon Tyne cases.

From the 7th to the 15th week of pregnancy the mean H.C.G. excretion in the hyperemesis patients was significantly lower than that in the normally pregnant women. From the 15th to the 20th week of pregnancy a significant difference between the two groups was not observed.

At all stages of pregnancy investigated the mean H.C.G. excretion of the group of normal subjects from Newcastle upon Tyne was significantly higher than that in the series of normal subjects from Edinburgh.

In the performance of the H.C.G. assays the skilled technical assistance of Miss M. A. Mackay and Miss K. Bach-Pedersen was much appreciated. We are also indebted to the nursing staffs at all the hospitals concerned, and in particular to Miss M. Grassick and Sister C. M. Campbell, from Aberdeen Maternity Hospital, for their assistance in collecting and dispatching samples.

APPENDIX

Pregnyl Sensitivity Test

One ampoule of "pregnyl" (human chorionic gonadotrophin B.P.) is made up with the diluting fluid supplied. The solution is well mixed and drawn up into a tuberculin syringe. An area on the patient's forearm is cleaned. An intradermal injection of 0.05 ml. of the pregnyl is then given into the prepared arm.

A positive reaction is indicated by the appearance immediately or within 24 hours of a red weal or flare round the area of the injection.

In the first 25 hyperemesis cases tested there were 20 positive results. In 35 control cases there were only five positive results. Subsequent correlation appeared to show that severe reactions tended to occur in patients in whom the H.C.G. level in urine was high.

Continued trial of the test, however, showed it to be unreliable because the extent of the reaction was extremely variable from one subject to another and because ultimately no definite correlation was found between the reaction and the H.C.G. level in urine. In view of these findings the test was discontinued in July, 1958.

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SALICYLATES AND GASTRO- INTESTINAL BLEEDING

ACETYSALICYLIC ACID AND ASPIRIN DERIVATIVES

BY

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The association between aspirin and haemorrhagic lesions of the gastro-intestinal tract has been observed by a number of investigators (Douthwaite and Lintott, 1938; Muir and Cossar, 1955; Alvarez and Summer-skill, 1958). The detection of occult blood in the stools of people taking salicylates by mouth was first recorded by Gregerson (1916). More recent investigations have extended this observation—chemical estimations (Lange, 1957; Stubbé, 1958); radioactive chromat studies (Scott *et al.*, 1961, reviewing the subject in some detail)—and have shown that approximately 70% of people bleed after taking aspirin. These findings initiated a search for a compound with all the valuable analgesic and anti-inflammatory properties of aspirin and which was free from associated gastro-intestinal blood loss. The present paper describes our findings with a number of preparations and derivatives of aspirin.

Material and Methods

Aspirin Preparations

The aspirin derivatives examined are listed in Table I, and Fig. 1 depicts their structural formulae. Further details of the less common preparations are given below. Some preparations were "buffered," and so the amount of acid required to restore the pH of a solution of the preparation to that of a saturated solution of acetyl-

FIG. 1.—Structural formulae of principal aspirin compounds examined.

salicylic acid is included in Table I as a measure of the antacid properties of the different formulations. In most instances studies were conducted by administering 15 gr. (972 mg.) of aspirin B.P. or its equivalent four times daily after food, usually for five days. Lower dosage was occasionally necessary because of salicylism, but all comparisons were made with equivalent doses

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of the different preparations. The method of administration accorded with the manufacturers' instructions, so that aspirin, aspirin glycine, aspirin anhydride, and aloxiprin (polyoxo-aluminium aspirin), were given as whole tablets, and the remainder were given in solution.

Physico-chemical Properties

Soluble Aspirin.—This was freshly dissolved in water to yield a solution of calcium acetylsalicylate.

Effervescent Aspirin.—This preparation contains a great excess of soluble alkali. The tablets were freshly dissolved in water to yield a solution of sodium aspirin.

S.A. 12.—This study was undertaken to test a hypothesis that aspirin would not cause bleeding if kept in solution in a sufficient dilution in the presence of an excess of antacid. The patients were instructed to dissolve each tablet in 80 ml. of water, and so to conform to our standard dosage schedule each patient thus had to drink 240 ml. of fluid four times daily for five days. A number of patients complained of the large volume of fluid required.

Calcium Aspirin Urea.—This complex is readily soluble in water. It is claimed that the replacement of the water of crystallization of calcium acetylsalicylate by urea confers greater stability, so that free salicylic acid formation is retarded. The complex dissociates in aqueous media, and thereafter its metabolism resembles that of aspirin itself, as has been shown by Bonard and Barbezat (1955).

Aspirin Glycine.—Physico-chemical evidence (Rapson *et al.*, 1959) suggests that the compounding of glycine with aspirin increases the rate of dissolution of acetylsalicylic acid. In addition glycine is adsorbed on aspirin particles, and this may affect the adhesion of aspirin to mucosal surfaces. A further effect is that the bitter taste of aspirin is masked.

Aspirin Anhydride.—It has been claimed that aspirin anhydride is non-acidic, that aspirin is formed only when the anhydride dissolves, and that at the pH of gastric juice salicylic acid liberation is negligible compared with that from aspirin (Garrett, 1959). *In vivo* this compound is less soluble in water than is acetylsalicylic acid, and it is only slowly hydrolysed by neutral or dilute acid solutions. Preliminary studies in man suggest a delay of about an hour in salicylate excretion after the administration of aspirin anhydride, but subsequently the excretion exceeds that after plain aspirin.

Aloxiprin.—This is an insoluble neutral compound of aluminium aspirin in polymeric form. *In vitro* the rate of solution of aspirin from aloxiprin is appreciably

slower than that of aspirin itself, especially in acid solutions. Preliminary studies in man suggest that it takes up to an hour longer than after aspirin *B.P.* for equivalent amounts of aloxiprin to be excreted, although the total excretion of salicylate in 24 hours is not significantly different (A. J. Cummings, 1961, personal communication). Two batches of this compound were examined. As there were small differences in the free aspirin content the results with the two batches are reported separately.

Subjects

Various aspirin preparations were given to 175 subjects, but 30 are not reported on further because no comparison with the effect of aspirin *B.P.* is available, and another similar instance is recorded only to demonstrate the most severe degree of salicylate-induced bleeding that we have observed. Thus there remain 144 subjects (37 male and 107 female), whose ages ranged from 6 to 81 years. The majority were patients admitted to the rheumatology or general medical wards of the hospital, or were attending the rheumatology out-patient clinic. Ninety-three patients had definite rheumatoid arthritis (A.R.A. criteria; Ropes *et al.*, 1957) and 41 suffered from other disorders; the remaining 10 subjects were normal volunteers. Many were studied because they presented an iron-deficiency anaemia after treatment with aspirin. Of the 134 patients, 24 gave a past or present history of peptic ulceration, and five of these had previously undergone partial gastrectomy. These patients with ulcers were selected because of the therapeutic problem they posed by requiring an analgesic for their rheumatic complaints.

Faecal Blood Loss

The faecal blood loss was measured quantitatively by estimating faecal radioactivity, having previously labelled the patient's erythrocytes with ^{51}Cr by a standard technique (Scott *et al.*, 1961). The blood was sufficiently radioactive for each study to last approximately 28 days, although with small patients the standard dose of ^{51}Cr permitted the studies to be continued for a longer period (as in Fig. 2). To compensate for variations in the duration of treatment with each drug, blood loss attributable to any particular compound was expressed as the mean loss per day of treatment (total faecal blood loss attributable to a drug divided by the number of days of treatment with the drug). This method of assessment differs slightly from that quoted by Scott *et al.*, who adopted an arbitrary criterion of what constituted associated loss, and divided the total

TABLE I.—Pharmaceutical Data on Preparations Examined

Preparation		Constituents* (Excluding Excipient)				Content* of Free		Acid Required to Reduce pH of Solution to 3 (Approx.) (mEq)
Title Used in Text	Proprietary Tablet Studied	Aspirin (mg.)	Carbonate (mg.)	Citric Acid (mg.)	Other (mg.)	Salicylic Acid (% w.w.)	Aspirin (% w.w.)	
Acetylsalicylic acid (aspirin)	—	324	—	—	—	0.036	—	—
Soluble aspirin	Disprin	324	Ca 97.2	32.4	Saccharin, 3.2	0.05	—	2
Effervescent aspirin	Solprin	324	NaH 1,625	966	—	1.8	—	19
S.A. 12	Alka-seltzer	324	Ca 366	31	Magnesium carb., 88	5.6	—	9
Calcium aspirin urea	Calurin†	≡324	—	—	Urea, 50	2.0	—	2
Aspirin glycine	Paynocil	648	—	—	Glycine 324	0.02	—	0.4
Aspirin anhydride	—	≡324	—	—	—	Nil	0.6	—
Aloxiprin	Palaprin	≡324	—	—	≡Al ₂ O ₃ , 80	1st batch 0.13 2nd batch 0.10	0.16 0.67	(2)‡

* As stated by the manufacturer. It was claimed that all the tablets conformed with the *B.P.* disintegration standard. The salicylic acid values are not strictly comparable, some being determined at the time of manufacture and others being determined after storage for varying periods.

† A preparation of similar composition is available in Europe under the name "ironin."
‡ This value represents the buffering capacity of the contained aluminium hydroxide. This is not available until the aspirin has been removed. Hence this value is not comparable with the other data, as this compound reacts only slowly with acid.

TABLE II.—Comparative Studies with Aspirin B.P.—Mean Blood Loss after a Number of Preparations of Aspirin

Preparation	Comparative Studies	Administered First		Mean Blood Loss on		Mean Difference (ml.)	Significance (t Test)
		Aspirin	Test Preparation	Aspirin	Test Preparation		
				(ml./Day of Treatment)			
Soluble aspirin	31	9	22	3.9	3.6	0.34±0.29	No P>0.2
Effervescent aspirin	15	13	2	5.5	2.5	3.00±1.09	Yes P<0.02
S.A. 12	18	12	6	3.6	3.0	0.58±0.52	No P>0.2
Calcium aspirin urea	15	14	1	5.5	5.2	0.27±1.29	No P>0.8
Aspirin glycine	15	15	0	4.3	5.4	1.10±1.49	No P>0.4
„ anhydride	22	18	4	3.9	4.6	0.68±0.69	No P>0.3
Aloxiprin .. { 1st batch ..	22	6	16	7.3	4.0	3.25±1.10	Yes P<0.01
	21	21	0	6.7	3.2	3.52±0.65	Yes P<0.001
All studies (cf. Fig. 4)	144 subjects	—	—	5.35	—	—	—

loss by the number of days over which the loss occurred (which was not necessarily the same as the number of days of treatment).

Comparative Bleeding Studies

Fig. 2 illustrates a typical series of studies in one patient. Drug-induced bleeding may continue for a

Fig. 2.—Comparative study of aspirin B.P. and aloxiprin in a woman aged 58 with rheumatoid arthritis. This patient was small in stature, and so the standard dose of ^{51}Cr resulted in greater radioactivity of the blood, enabling the studies to be continued for a longer period than usual. The apparent small difference between blood loss following the two courses of aloxiprin is probably attributable to changes in the margin of mathematical accuracy due to the diminishing radioactivity of the patient's blood.

Fig. 3.—Comparative studies of aspirin preparations when additional therapy was required in a woman aged 40 with rheumatoid arthritis. Paracetamol did not control this patient's symptoms and so hydroxyphenylbutazone was given in addition. This patient had undergone comparative studies of aspirin and soluble aspirin 18 months prior to this study. On that earlier occasion the mean loss after both preparations was just under 4 ml. per day of treatment.

number of days after a drug has been stopped, and periods of treatment were therefore separated by periods without drugs until faecal blood loss had returned to control levels. Some patients had to remain on other maintenance therapy and some, whose symptoms were so severe that periods without drugs were unjustifiable, were given other anti-inflammatory and analgesic compounds. In all such cases the control observations, and the return of faecal blood loss to these levels after each salicylate study, confirmed that the additional medication did not cause bleeding. Fig. 3 illustrates such a case. At the beginning of the investigation we invited comments on side-effects with the different preparations, and thereafter we noted what observations the patients volunteered. We deliberately avoided asking questions during the studies so that greater weight could be attached to the patients' observations. The order in which preparations were administered was not controlled. If a patient was already taking a salicylate, this preparation was continued for the first study (as in Fig. 3). If treatment had not been started, aspirin was usually given first. In either case, if bleeding was detected the patient was then tested with another preparation. When the same compound was administered twice to the same subject (as in Fig. 2) a comparison was based on the combined results of the two periods.

Results

Comparative Bleeding Studies

Fig. 4 shows the degree of blood loss after the administration of aspirin in the group of subjects studied. The results of the comparative studies are set out in Table II. Faecal blood loss was reduced significantly and to a similar extent after both effervescent aspirin and aloxiprin, although the reduction was not

Fig. 4.—Mean faecal blood loss after aspirin in 144 subjects. This distribution is slightly biased towards the larger bleeders owing to the selection of a small proportion of the subjects because they had been taking large doses of salicylates and had an iron-deficiency anaemia.

uniform in all subjects. Fig. 5 depicts the scatter of differences in blood loss after some of the preparations studied. This shows that in nearly two-thirds of the subjects there was little difference between the blood loss after aspirin and that after the effervescent compound or aloxiprin, whereas in the remaining subjects there was a considerable reduction. Nevertheless, even when these two compounds caused much less bleeding the blood loss they did cause was still considerable in some of the patients. In addition, the reduction was not directly related to the severity of aspirin bleeding; in some patients who lost 15 ml. per day of treatment after aspirin, the effervescent preparation or aloxiprin caused losses of up to 13 ml. per day of treatment.

There was no significant difference between the degree of bleeding observed after aspirin *B.P.* and all the other formulations of aspirin that were studied. A similar degree of bleeding was also observed after "aspro" (3), "anadin" (1), Beecham's powders (1), A.P.C. (2), compound codeine (14, including 2 after "codis" and 1 after "veganin"), and codeine-aspirin—a Hammersmith Hospital preparation, each tablet containing aspirin, $7\frac{1}{2}$ gr. (486 g.), and codeine, $\frac{1}{8}$ gr. (8 mg.) (8)—the figures in parentheses denoting the number of patients studied with these preparations. Fig. 6 demonstrates the most severe bleeding we have observed. This patient took the standard five-day course of S.A. 12, and during the ensuing three weeks she lost a total of 419 ml. of blood (a mean of 84 ml. per day of treatment). When the blood loss had ceased her blood was insufficiently radioactive to permit an accurate comparative study of aspirin *B.P.*

FIG. 5.—Scatter of differences in blood loss after some of the preparations of aspirin examined.

Patients' Comments

Apart from the following two exceptions, nothing was volunteered about preference for aspirin or any of the other preparations examined.

Aspirin Anhydride.—These tablets were unpopular, and in a sequence of studies this preparation was singled out for unfavourable comment by seven patients. Three of these patients, two of whom had peptic ulcers, stopped the course of the drug early because of the severity of their dyspepsia, although they tolerated the full course of aspirin without complaint. Of greater note was the complaint by five other patients that aspirin anhydride did not produce such satisfactory relief of their symptoms as did aspirin *B.P.* The studies were not planned to assess therapeutic potency, but we soon found that the patients with active rheumatoid disease fairly readily enabled us to identify those compounds with lesser anti-inflammatory properties. Of the 22 patients studied with aspirin anhydride, 14 suffered from rheumatoid arthritis, though not all of them were in an active phase. Thus aspirin anhydride was less effective in more than 30% of the trials which might have revealed differences in therapeutic potency.

Aloxiprin.—This preparation was well tolerated. Two patients with duodenal ulcers experienced dyspepsia when taking both aspirin and aloxiprin, but eight others with gastric or duodenal ulcers accepted the new compound without complaint. One other patient preferred aloxiprin as she developed indigestion after taking plain aspirin. A few patients complained of constipation during or shortly after taking aloxiprin. A review of stools received throughout the studies enabled us to make an objective assessment of this complaint. One-third of the patients did show a change of bowel habit attributable to aloxiprin, whereas during the remainder of the studies their bowel habit was constant. This change did not amount to more than the occasional day passing without a bowel action, and occurred during or within three days of stopping the course of aloxiprin.

FIG. 6.—Large-scale bleeding after an aspirin preparation in a woman aged 50 with degenerative joint disease. Throughout the period of study this patient experienced no symptoms apart from those attributable to her degenerative joint disease. She had no history of dyspepsia, and a subsequent barium-meal examination was negative. Four months later she was studied again, and on this occasion she lost 177 ml. of blood in the stools after five days of aspirin *B.P.* (a mean of 35 ml. per day of treatment).

Thirty of the patients studied suffered from rheumatoid arthritis, and in all these aloxiprin controlled the disease in as satisfactory a manner as did aspirin *B.P.*, and two patients volunteered that aloxiprin gave them greater relief.

General Observations

There was no association between dyspepsia and bleeding—some patients who experienced severe dyspepsia after taking aspirin were non-bleeders, and others were big bleeders and yet did not develop any gastro-intestinal symptoms.

As a group, patients with rheumatic diseases behaved no differently from a group of normal people with regard to aspirin-induced gastro-intestinal bleeding.

Similarly, those with peptic ulcers did not seem to respond at all differently from those with a clinically normal bowel (Wood *et al.*, 1961). For this reason no attempt had been made to analyse the results with the different preparations according to the patients' diseases.

The response to aspirin was a relatively constant and reproducible phenomenon (cf. the two studies with the same compound shown in Fig. 2, and also the earlier studies on the patient demonstrated in Fig. 3).

Previous salicylate ingestion did not appear to modify the response (cf. the studies before and after aspirin shown in Fig. 2, and also the response to soluble aspirin by the patient in Fig. 3). This patient had been taking soluble aspirin for many months, and the first period of study shown was during the continuation of this regime). When this was taken in conjunction with the variations in the order of administration of the different preparations, as noted in Table II, it seems reasonable to suppose that the order of administration does not have any significant effect on the resultant bleeding.

Discussion

The association of aspirin with other organic molecules may affect the stability, solubility, and palatability of the preparation, but we have found that on ingestion these complexes did not differ from aspirin *B.P.* in the magnitude of the resultant gastro-intestinal blood loss. Similarly the salts of acetylsalicylic acid did not differ from aspirin itself in this respect. This finding is supported by many of the early studies on this problem, it is implicit in the work of Grossman *et al.* (1961), and it has been confirmed by Stubbé *et al.* (1961, 1962). In contrast, Pierson *et al.* (1961) claimed that calcium aspirin caused less bleeding than did acetylsalicylic acid. The difference to which they attached significance was between the average loss after calcium aspirin urea in 24 subjects (2.1 ml. a day) and the average loss after plain aspirin in 148 subjects (4.7 ml. a day). Such a difference may be observed between two different groups treated with the same preparation (Table II, column 5). The same criticism can be applied to all the conclusions of Pierson and his colleagues, which were based on comparisons with the response to aspirin of their whole group of subjects. Nevertheless, it is interesting to note the similarity of their figure for the overall mean blood loss on aspirin to that which we observed.

The suggestion that sodium or calcium aspirin may be less irritant to the bowel is based on the solubility

of these salts in water, so that they can be ingested in solution. Similar reasoning is employed to explain a greater subjective tolerance for soluble aspirin. Some have claimed that soluble and buffered preparations cause less dyspepsia—for example, Vining and Kersley (1957)—although carefully controlled studies have failed to support this (Batterman, 1958; Cronk, 1958). It is our experience that most patients who claim to be intolerant of aspirin can, in fact, tolerate the drug if they are unaware of what it is. There remains a small proportion of people who get severe and reproducible dyspepsia, and we have found that this dyspepsia is not affected by substituting more elegant preparations.

In solution the salts of aspirin would ionize, and at gastric pH free acetylsalicylic acid would precipitate, owing to its sparing solubility. It is difficult to find a satisfactory physiological explanation for the readier acceptance of soluble preparations. We have found that dyspepsia is unrelated to bleeding, and in the development of dyspepsia the presence of undissolved particles may be of importance. On the other hand, aspirin and its salts may have an identical effect on the gastro-intestinal tract, and the difference may occur at a more subjective level. Soluble and buffered aspirins are pleasanter to take, and in itself this would help to condition a reduction in any resultant dyspepsia. The fact that rheumatic patients are the only people who commonly need to take very large doses of aspirin may explain their apparently more frequent intolerance, because palatability becomes an even larger factor. This must lead one to question whether, in view of the much greater cost of soluble and buffered aspirins, it is justifiable to make substitutions for aspirin *B.P.* without greater efforts than are usually made to achieve acceptance of the simple pharmacopoeial preparation.

The situation is altered if a large quantity of antacid is administered at the same time as aspirin. S.A. 12, with an excess of 9 mEq of antacid, did not differ from plain aspirin with regard to induced faecal blood loss. On the other hand, effervescent aspirin, with an antacid content of 19 mEq, was associated with a reduction in blood loss. This finding has been confirmed by Stubbé *et al.* (1961), who, with a chemical determination, found no occult blood in most of their patients after taking effervescent aspirin. With ^{51}Cr we have demonstrated that bleeding does occur, but that it is reduced in amount. Stubbé's effervescent aspirin formulation was that available in the United States, and contained slightly more sodium bicarbonate and citric acid, and also small amounts of calcium phosphate and magnesium oxide. Stubbé and his colleagues noted diarrhoea after large doses of effervescent aspirin. We administered similar doses, but there was no increase in the frequency of the subjects' bowel actions. This difference could be due to the small quantities of magnesium. Matsumoto and Grossman (1959) were able to cause a similar reduction in the volume of blood lost by administering calcium carbonate or aluminium hydroxide gel every hour the patient was awake during the periods when aspirin was given. They also found that the administration of aspirin with a small amount of sodium bicarbonate (approximately 4 mEq of excess antacid per tablet) in 100 ml. of water did not reduce the volume of aspirin-induced bleeding.

It is thus possible to conclude that antacid modifies the response by virtue of its neutralizing effect, as the

antacid may be soluble or insoluble, and need not contain a carbonate or bicarbonate ion. In the presence of an excess of potential buffering material it is highly probable that a large proportion of the aspirin would be present in the form of its salt, either calcium or sodium depending on the cation of the antacid. Hogben *et al.* (1957) have suggested that only undissociated acetylsalicylic acid is absorbed from the stomach, and thus the excess of antacid could reduce gastric absorption of aspirin. This suggests that gastric bleeding may be, in part, dependent upon absorption of aspirin by the gastric mucosa.

That this is not the only factor involved is suggested by the variations in the response to effervescent aspirin. On the other hand, to reduce gastric absorption in the manner suggested, the formation of undissociated aspirin must be prevented in that layer of the gastric contents immediately in contact with the mucosal cells. This could explain the large amount of antacid required, and it is possible that in those subjects in whom no reduction in bleeding occurred there was insufficient antacid to ensure the presence of ionized aspirin at the mucosal interface. Proof of this hypothesis is difficult to obtain, partly because existing techniques for the estimation of serum salicylate levels are insufficiently precise when the concentration of salicylate is small, but also because it is known that effervescent aspirin enhances the absorption of aspirin by the bowel. The presence of an excess of sodium bicarbonate promotes gastric emptying, and it is difficult to determine whether duodenal absorption contributes to the early rise of plasma salicylate levels observed soon after the administration of effervescent aspirin.

That bleeding may be due to the process of absorption of aspirin in the stomach conflicts with Levy's (1961) hypothesis that the more rapidly absorbed formulations would be less irritant to the bowel. His data were derived from studies relating tablet dissolution and absorption rates, but in extending his hypothesis to explain gastro-intestinal bleeding he quotes the work of Watson and Pierson (1960); their paper was a preliminary presentation of some of the data reported subsequently by Pierson *et al.* (1961), the validity of which we have already questioned. The corollary of Levy's hypothesis is that less soluble products would be more prone to present particulate aspirin to irritate the stomach. This, too, conflicts with our findings. A whole tablet of aspirin B.P., a "flash" dispersal preparation (aspirin glycine), and a solution of aspirin (S.A. 12) all caused the same degree of bleeding. This suggests that the presence of particles of an aspirin tablet bears no direct relation to the incidence or magnitude of gastro-intestinal blood loss, and the findings with S.A. 12 also suggest that the bulk of the draught in which effervescent aspirin was administered was not a factor concerned in the reduction of bleeding. Recent gastroscopic studies by Weiss *et al.* (1961) also suggest that particles can be exonerated from any significant role in causing bleeding.

The interest in aloxiprin is threefold. First of all, although this compound does cause gastro-intestinal bleeding, there is a significant reduction in the volume of blood lost compared with that following aspirin. Secondly, the delay in excretion of this compound may indicate that most of it passes through the stomach without being absorbed. The more rapid liberation of aspirin from aloxiprin in an alkaline milieu would also

support the idea that absorption from the small bowel is more likely, and this different site of absorption may be the cause of the reduced bleeding. The findings of Scott *et al.* (1961) and of Stubbé *et al.* (1961) with enteric-coated preparations suggest that the small bowel can be the site of blood loss, but that in general the amount lost is less. Thirdly, the chemical basis for a reduction in gastric absorption of aloxiprin presumably lies in its complex polymeric structure. Certainly the chemical linkage of this compound is unlike that of any other preparation studied, and this was the only aspirin compound which on its own was associated with a reduction in bleeding. The occurrence of constipation attributable to this compound may be due to the content of aluminium (and in this context we must point out that we have not observed that constipation affects the total amount of blood lost).

The therapeutic use of aspirin anhydride was first advocated by Bayer and Company in 1908, when they patented methods for its preparation. Despite some recent work by the Upjohn Company in the United States, no pharmaceutical firm has so far launched this product on the market. Our results suggest that this compound has lesser analgesic and anti-inflammatory properties, and this has been confirmed in animals (Nicholas Research Institute, 1961, personal communication). We have already referred to the work of Garrett (1959) on this compound. Apart from the fact that his evidence is not entirely convincing, there is also no evidence that the reasons he advances for the superiority of aspirin anhydride have any relevance. It is difficult to interpret the lesser therapeutic activity of this compound with the lack of data on whether it is absorbed intact or as acetylsalicylic acid. It may be that the anhydride molecule itself is therapeutically less active. Alternatively, the compound may undergo hydrolysis, and one of the aspirin molecules may be converted into an inactive form in the process, so that the result would be a halving of the effectiveness of the administered dose. Kyriakopoulos *et al.* (1960) claimed that aspirin anhydride induced less gastro-intestinal bleeding than did aspirin itself, but they employed chemical estimations for occult blood and had a high proportion of placebo bleeders. We cannot confirm their observations, and the work of Stubbé *et al.* (1961) is in agreement with ours.

Summary

Most commonly available preparations of aspirin, including its soluble salts and the complexes with other organic molecules, are equally potent causes of gastro-intestinal haemorrhage.

Effervescent aspirin, which contains a large excess of sodium bicarbonate, causes significantly less bleeding, although this observation has little therapeutic application. A possible explanation for this observation is advanced.

A new compound, aloxiprin (polyoxo-aluminium aspirin) is associated with a similar reduction in blood loss, although the reduction is not uniform in all subjects. This preparation appears to be a satisfactory substitute for plain aspirin, and does represent a slight advance towards our ideal of an aspirin that is free from associated blood loss.

The status of aspirin anhydride is reviewed. This compound is not always effective therapeutically, and causes as much gastro-intestinal bleeding as does aspirin itself.

A solution of aspirin is as potent a cause of blood loss as the *B.P.* tablet of aspirin. This suggests that undissolved tablet particles have no direct relevance to this problem.

It is suggested that gastric absorption of undissociated acetylsalicylic acid is one of the factors concerned in causing blood loss. This leads us to question the validity of much prevailing thought about physico-chemical differences between different preparations of aspirin.

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Mental Health, the journal of the National Association for Mental Health, takes "Psychiatry and the General Practitioner" as the theme for its winter issue. Among the general practitioners contributing are Dr. L. M. Franklin, Dr. J. Horder, and Dr. C. A. Watts. Dr. T. P. Rees surveys training courses and opportunities in this field. Other features include an account of a nation-wide survey of clubs for the mentally disordered given by Dr. Russell Barton at the N.A.M.H.'s annual general meeting. Some account is given of the development in mental health in places as far apart as Poland and Nigeria. (Price 2s. 6d. from N.A.M.H., 39 Queen Anne Street, London W.1.)

ASPIRIN PREPARATIONS AND THEIR NOXIOUS EFFECT ON THE GASTRO-INTESTINAL TRACT

BY

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It has long been emphasized that aspirin may induce massive gastro-intestinal bleeding due to gastritis or a peptic ulcer (Douthwaite and Lintott, 1938; Hurst and Lintott, 1939; Hurst, 1943; Douthwaite, 1954; Muir and Cossar, 1955, 1959; Brown and Mitchell, 1956; Kelly, 1956; Lange, 1957; Alvarez and Summerskill, 1958). Several recent studies show that tests for occult blood in faeces often become positive when aspirin is given (Lange, 1957; Stubbé, 1957, 1958; Alvarez and Summerskill, 1958; Matsumoto and Grossman, 1959; Porter *et al.*, 1959; Watson and Pierson, 1960; Holt, 1960).

An occult blood loss in the faeces, caused by the use of aspirin, was found by us in 257 (61%) of a group of 421 patients in hospital mainly because of some rheumatic complaint. This group consisted of 128 men and 293 women. Patients with a history of stomach trouble were excluded from treatment with aspirin. In 40 control cases given aspirin, about the same percentage with occult blood loss was found. In general, the quantity of aspirin given was 1,500 to 3,000 mg. a day, though a few cases received larger amounts as an exception. This investigation was carried out in a manner already described (Stubbé, 1957, 1958).

Practically all investigators now agree that a direct local irritation of the gastric mucosa is the cause of occult blood loss, although an irritation of the intestinal mucosa, so far as we know, could never be ruled out.

The amount of blood lost may vary considerably. Baragar and Duthie (1960) found in 244 patients with rheumatoid arthritis, most of whom were said to have used aspirin regularly for six years, no obvious decrease but a significant rise in the haemoglobin content. In what degree other factors, such as iron therapy or decrease in activity of the rheumatic process during this period, had any influence was not stated. On the other hand, Kelly (1956) described three cases and Summerskill and Alvarez (1958) two cases of severe iron-deficiency anaemia due to gastro-intestinal haemorrhage associated with the taking of aspirin. Matsumoto and Grossman (1959) gave 3 g. of aspirin daily to 38 persons for three or six days: 15 were found to have had a blood loss of less than 2 ml. a day, 16 a loss of 2 to 5 ml. a day, and 7 a loss of more than 5 ml. daily.

Porter *et al.* (1959) observed, in 11 patients with some rheumatic complaint who were given about 4 g. of aspirin daily, an average blood loss of under 5 ml. a day. In four patients with an iron-deficiency anaemia, however, they found a blood loss of more than 5 ml. (in one female patient even 60 ml.) a day during the