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ASPIRIN AND ULCER

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It has been known for many years that the taking of aspirin may cause dyspepsia. The observations of Douthwaite (1938), Douthwaite and Lintott (1938), and Hurst and Lintott (1939) indicated that serious gastric haemorrhage could also occur following the use of aspirin, particularly on an empty stomach.

Douthwaite and Lintott made a detailed gastroscopic study of the reactions of the gastric mucosa to the ingestion of gastric irritants, with particular reference to aspirin. They examined 16 unselected patients shortly after the administration of 15 gr. (1 g.) of crushed aspirin in 1 oz. (28 ml.) of water and found that 13 of them developed a mucosal reaction varying from slight hyperaemia to intense congestion with submucous haemorrhages. These reactions were localized to the area immediately surrounding adherent aspirin particles and were maximal on the lesser curvature. A further five patients were gastroscopied after the administration of 15 gr. (1 g.) of calcium aspirin, and one showed a very mild reactive hyperaemia only. To ascertain if free salicylic acid, known to be present in certain brands of aspirin tablets, was responsible for the reaction, two further patients were examined by the same technique, substituting salicylic acid for aspirin. Both showed a positive reaction, but in neither case was it more intense than that which had frequently been seen to result from aspirin alone.

Hurst and Lintott gastroscopied a patient with a history of repeated haematemesis and actually saw bleeding occurring from the intensely hyperaemic areas surrounding two large portions of aspirin tablet.

Wolf and Wolff (1943) were unable to produce an aspirin reaction in the gastric mucosa of their subject Tom, and Paul (1943) was unable to find any evidence of gastric irritation from aspirin on carrying out 1,000 gastroscopies. This latter work has recently been criticized by Douthwaite (1954) on technical grounds.

The present investigation, prompted by the personal experience of one of us, was started in 1947. It was decided to investigate fully the possible harmful effects of aspirin on the stomach, particularly in patients with peptic ulcer.

Experimental

A group of 20 patients, each suffering from radiologically confirmed peptic ulceration, were selected, and in each of them three standard caffeine-citrate fractional test meal examinations were performed at intervals of a few days. The first test was done normally to serve as a control. After the removal of the fasting juice during the second and third meals, two bland calcium lactate tablets and two 5-gr. (0.32-g.) aspirin tablets were given respectively, uncrushed, with a little water. Specimens were removed at half-hourly intervals until the stomach was empty. Each specimen was tested for free and total acidity and examined for blood chemically and by naked eye. In 15 of these patients faecal occult blood tests before and after the aspirin test meal were made by the Gregersen method. The simple fractional test-meal was chosen with a full knowledge of its limitations in place of the more accurate serial test meal, since the chief interest in each specimen was the presence or absence of blood and not its chemical content.

It will be seen from Table I that aspirin tended to increase gastric acidity and that evidence of gastric irritation, as shown by the presence of blood-stained mucus in the test-meal specimens, was commonly present.

Thus in five patients (Cases 1, 3, 5, 6, and 20) blood-staining of the specimens was observed during the aspirin test meal alone. In one (Case 7) it was much greater than had been observed during the calcium lactate test meal; in two (Cases 10 and 15) it was similar; and in one (Case 14) it was less. The blood seen with the control test meals, presumably traumatic in origin, was often fresh red blood appearing in the syringe at the end of withdrawal of a specimen. The blood found in the aspirin test meals was in the form of blood-stained mucus and clots of altered blood, and once it had appeared it remained constant and sometimes increased to the end of the test.

A further point of interest was the conversion by aspirin of a previously consistently negative test for faecal occult blood to a strongly positive one in three patients (Cases 3, 5, and 6).

Pathology

In order to study directly the effect of aspirin on the stomach two uncrushed 5-gr. (0.32-g.) aspirin tablets with a little water were given to a series of patients approximately two hours prior to gastrectomy for peptic ulceration. Shortly after their removal the specimens were examined macroscopically for evidence of gastric irritation, and later microscopically. An initial 20 gastrectomy specimens were studied before these investigations to gain some knowledge of the effect of trauma, the presence of gastritis, etc., in routine gastrectomy specimens. In the first 20 patients an ordinary commercial brand of aspirin was given, in the second 20 a specially hard type of aspirin tablet was used (see below), and in the last 20 soluble calcium aspirin ("disprin") was given. Gentle gastric aspiration, but not lavage, was done by the anaesthetist just before operation, but it was felt that this could not alter significantly any evidence of gastric irritation.

Of the 20 patients who received ordinary commercial brand aspirin, 8 showed no evidence of mucosal irritation. A little mucosal oedema and congestion, a few scattered petechial haemorrhages, especially near the more massive interstitial haemorrhages of clamp marks, and some flakes of adherent mucus were present, but these were also present in a few of the initial control group and were disregarded. In the remaining 12 patients evidence of mucosal irritation was present macroscopically in the form of an acute gastritis. In 9 of these the condition was relatively mild, but

TABLE I.—Effect of Aspirin on Fractional Test Meal

Case No.	Type of Ulcer	Previous Aspirin Dyspepsia	Standard Test Meal	Calcium Lactate Test Meal	Aspirin Test Meal	F.O.B.	
						Before Aspirin Test Meal	After Aspirin Test Meal
1	Duodenal	Yes	Hyperchlorhydria	+++. No blood	Hyperchlorhydria. Blood-stained mucous (+) in specimens 2-5	+	+++
2	Duodenal with stenosis	Did not know	Plateau curve. Hyperchlorhydria	+. No blood	Hyperchlorhydria +. No blood	+	+
3	Duodenal	None	Plateau curve. Hyperchlorhydria	+++. No blood	Plateau curve. Hyperchlorhydria ++. A little blood-stained mucous (+) in specimens 1-2	—	+++
4	"	"	Hyperchlorhydria	+++. No blood	Hyperchlorhydria +++. No blood	—	—
5	"	Yes	Hyperchlorhydria	+++. No blood	Hyperchlorhydria +++. All specimens grossly contaminated with blood-stained mucus and altered blood (+++)	—	+++
6	Gastric	None	Low acidity. No blood	Hyperchlorhydria +. No blood	Hyperchlorhydria ++. Last 4 specimens markedly contaminated with clots of altered blood and blood-stained mucus (+)	—	+++
7	Duodenal	Never taken any	Low acidity. A little altered blood (+) in three middle specimens	Hyperchlorhydria ++. A little altered blood (+) in all specimens	Hyperchlorhydria ++. All specimens showed considerable blood-stained mucus and threads of altered blood (+++)	—	—
8	Stomal	"None"	Normal acidity. No blood	Hyperchlorhydria ++. A little fresh blood in last 3 specimens (+)	Normal acidity. No blood	—	—
9	Duodenal	"None"	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. A little fresh blood in last 3 specimens (+)	Hyperchlorhydria ++. Last 4 specimens showed flecks of clotted blood and blood-stained mucus (+)	—	+
10	"	"	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. A little fresh blood in last 3 specimens (+)	Hyperchlorhydria ++. No blood	+	+
11	"	"	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. A little fresh blood in last 3 specimens (+)	Hyperchlorhydria ++. No blood	+	+
12	"	"	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. A little fresh blood in last 3 specimens (+)	Hyperchlorhydria ++. No blood	+	+
13	"	Yes	Hyperchlorhydria ++. A little altered blood in all specimens (+)	Hyperchlorhydria ++. No blood	Normal acidity. No blood	—	—
14	"	Not sure	Hyperchlorhydria ++. A little altered blood in all specimens (+)	Hyperchlorhydria ++. No blood	Hyperchlorhydria +++. No blood	—	—
15	Duodenal with gastroenterostomy	Yes	Hyperchlorhydria ++. Considerable blood-staining of all specimens (+)	Hyperchlorhydria ++. No blood	Hyperchlorhydria +++. Altered blood in all specimens (+)	—	—
16	Duodenal	Never taken any	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. No blood	+	—
17	Gastric	"Yes"	Normal acidity. No blood	Hyperchlorhydria ++. No blood	Low acidity. No blood	+	+++
18	Duodenal + gastric	"Yes"	Low acidity. No blood	Hyperchlorhydria ++. No blood	" " " "	—	—
19	Gastric	None	Very low acidity. No blood	Achlorhydria. No blood	Very low acidity. No blood	+	+++
20	Duodenal	Yes	Hyperchlorhydria ++. No blood	Hyperchlorhydria ++. No blood	Hyperchlorhydria +++. Altered blood in all specimens (+)	+	+++

in 3 it was severe. The lesion was always most marked in the pyloric antrum and on the lesser curvature (see Fig. 1). It was patchy and varied in intensity in the same specimen. The mucosa was congested and oedematous, with flakes of adherent mucus containing aspirin fragments and often altered blood. Multiple erosions were visible to the naked eye in 5 of them, and microscopically in all. They were maximal along the summits of the rugae, frequently contained a tiny fragment of aspirin, and were surrounded by an areola of intense hyperaemia.

Microscopically the lesion showed congestion of mucosal capillaries and oedema of interstitial tissues with polymorphonuclear and round-cell infiltration. Glandular erosion, flattening, and dark staining of the mucosal epithelium with polymorphonuclear-containing vacuoles between cells and typical erosions were all seen—that is, the picture was typical of an acute erosive gastritis (Magnus). In the 3 specimens in which this was severe the aspirin left in the stomach was in large portions and the mucous reaction was noticeably poor. The erosions were larger and were obviously produced by firmly adherent particles of aspirin which remained *in situ* and had to be picked from the erosion in order to see it.

In one of these cases half an aspirin tablet was found deeply embedded in the mucosa of the greater curvature lying beneath the overlapping edge of an oedematous and congested ruga (see Fig. 2). It proved impossible to pick this out without damaging the specimen. When it was eventually removed a lesion showing the features of an acute peptic ulcer rather than a simple erosion was visible. Its floor was covered with a greyish fibrinous exudate and it penetrated into the submucosa. A localized serosal congestion indicated its site.

Of the 20 patients who received specially hard aspirin tablets, 12 showed no definite evidence of gastric irritation. The remaining 8 showed typical acute erosive gastritis, mild in 3 cases, moderately severe in 5. No severe lesions as described above were seen in this series. These findings were unexpected in view of the frequency with which large

FIG. 1

FIG. 2

FIG. 1.—Adherent aspirin particles have been removed from the gastric mucosa of the pyloric antrum, revealing a few erosions, in this case rather circular and punched-out in appearance. The congestion is poorly shown in this type of photograph. FIG. 2.—The small aspirin ulcer is clearly visible, with a crust of aspirin still *in situ*.

portions of residual aspirin were found in the stomach. It was anticipated, as a result of the findings in the first series of cases studied, that this would increase the incidence of the more severe type of lesion. The reason for this failure to do so was obvious, however, when the extent of the mucous reactions in this series was observed. In almost all cases the residual aspirin was coated in a thick capsule of dense mucus. In one case practically an entire aspirin tablet was found so coated. It is reasonable to assume that defective mucous reaction was an important factor in causing the severe lesion observed in the three cases of the first series.

Of the 20 patients who received soluble aspirin 18 showed no mucosal reaction. In the remaining two a very mild reaction was seen, not definitely classified as abnormal.

Microscopically the majority of these 60 specimens showed a chronic gastritis, severe in the 7 showing gastric ulceration and relatively mild in the remaining 53 patients with duodenal ulceration.

Acute erosive gastritis is a known complication of gastric ulceration. Magnus (1946) gives a figure of 7% for its presence macroscopically in a series of 284 gastrectomy specimens, but Puhl (1927) (27%) and Konjetzny (1930) (100%) give a much higher figure. Magnus (1946) admits that, microscopically, a mild acute erosive gastritis of the pyloric antrum is commonly seen in gastric ulcer specimens, but denies its frequency on naked-eye examination.

In the case of duodenal ulceration, macroscopically evident acute erosive gastritis is rarely seen. Magnus (1946) found it only very occasionally in 256 gastrectomy specimens, and it was always very mild. Walters and Sebening (1932) agree with this conclusion, but Puhl (1927) found it more frequently.

The specimens in this series showing the most severe acute erosive gastritis were all from patients with duodenal ulceration. Moreover, the erosions were obviously the result of the local irritant action of aspirin, since they often took the shape of the aspirin granule, which remained *in situ*.

As a preliminary investigation approximately 300 people, representing an average cross-section of the community, were questioned about aspirin intolerance without reference to their previous medical history. Approximately 1 in 20 confessed that aspirin gave them dyspepsia—heartburn, sometimes nausea, and occasionally epigastric discomfort. The following clinical investigations were then made:

Clinical Investigations

1. Aspirin Intolerance in Peptic Ulcer

A series of 318 patients suffering from peptic ulcer were questioned on a similar point. All of these had a definite opinion to express. As in the control series above, if they had not taken aspirin often enough to be able to express such an opinion they were not included.

Approximately one-third (110) were well aware that aspirin could be taken only at the risk of a bout of dyspepsia. Again the chief symptom was heartburn, but some of them were sure that ulcer pain could be aggravated or restarted by taking aspirin on an empty stomach, and so avoided it entirely.

2. Aspirin as a Cause of Breakdown of Peptic Ulcer

A group of 83 patients suffering from peptic ulceration were selected on the basis of their past history. Each of them had periodic bouts of ulcer pain with long complete remissions. It was hoped that by detailed questioning some idea of the factors causing their latest clear-cut breakdown could be gained, with particular reference to the taking of aspirin. Thirty-four of these patients suffered from gastric ulcer and the remainder from duodenal ulcer. Recurrence of symptoms could in most cases be pin-pointed to a particular day, and questions were directed to the period immediately preceding it. Fourteen gastric ulcer patients and 19 duodenal ulcer patients admitted to taking aspirin less

than 24 hours before the recurrence of their symptoms. Moreover, 8 of these patients blamed aspirin because of similar previous experiences, some of them having been misled by the wording of the advertisements of a popular brand, others taking headache powders which they did not know contained aspirin.

The following two histories are typical of the group:

Case 1.—A woman aged 67 had suffered from gastric ulceration with haematemesis at the age of 21. Symptoms had lasted for a year intermittently after her discharge from hospital and then completely disappeared. She remained healthy until February, 1952, when osteoarthritis of her right hip developed. The pain became severe and she consulted her own doctor in July, 1952. He prescribed aspirin, two tablets three times a day after meals—the first time the patient, to her knowledge, had ever taken aspirin. On the first day of this regime she developed dyspepsia of gastric ulcer type—epigastric pain and vomiting 20 minutes after a meal. This persisted for four days, during which time she stopped taking aspirin, and culminated in a moderately severe haematemesis, for which she was admitted to hospital. Radiologically a small lesser-curve gastric ulcer was subsequently demonstrated; this healed rapidly on routine treatment, and has remained healed to date.

Case 2.—A garage mechanic aged 29 had suffered from duodenal ulcer for 11 years. His symptoms had improved on routine medical treatment, and in the previous four years he had had only three bouts of ulcer dyspepsia, each lasting about a fortnight. The bout causing his visit to hospital started on July 16, 1953. For four days prior to this he had taken two aspirin tablets night and morning for "rheumatism of the back." His penultimate bout was a year previously, and immediately before it he had taken aspirin for a few days to relieve the pain of a crushed finger. He remembered taking aspirin four years previously for a strained muscle, and recalled that it coincided with his only period off work with ulcer symptoms. In the previous four years, therefore, his three bouts of ulcer dyspepsia had been immediately preceded by the only periods in which he had taken aspirin.

3. Aspirin as a Cause of Chronic Dyspepsia

In seven years 15 patients (11 female and 4 male) with major dyspepsia were seen who were habitual aspirin takers, and who were cured of their dyspepsia by its withdrawal. Chronic heartburn was a prominent symptom in each, but epigastric distress after meals, flatulence, nausea, and vomiting were all occasionally present. Moreover, three of these patients gave a history of gastric bleeding—a single episode in one, but repeated in the other two. As the result, each of these three patients was regarded as a peptic ulcer case in spite of frequent negative x-ray films of the upper alimentary tract, and one (Case 3) had a laparotomy for possible gastrectomy.

Case 3.—A woman aged 47 had had dyspepsia for 11 years. This consisted of upper abdominal discomfort immediately after meals, heartburn, nausea, and occasional vomiting. She had spent four periods in different hospitals during this time because of haematemesis and melaena. Each haemorrhage was relatively mild, but it recurred on one occasion several times in the course of a few days (September, 1949). Each time a subsequent barium-meal examination was negative, and no cause could be found for her dyspepsia and haemorrhage, although a gastric ulcer was suspected on every occasion. On her fourth admission, to a larger hospital, in May, 1950, a gastroscopic examination was made two weeks after her haemorrhage. No ulcer was definitely seen, but an area of mucosal hyperaemia was seen low down on the lesser curvature, possibly indicating the site of an ulcer invisible to the gastroscopist. In view of her history a laparotomy was done; but apparently nothing was found to warrant resection, since she was discharged home shortly afterwards with a tentative diagnosis of gastric ulcer.

Within a few weeks her dyspepsia started again and she was once more referred to hospital. On this occasion she volunteered information that she had taken at least one, and often as many as three, headache powders a day for many years to "settle her nerves." She herself suspected that this was the cause of her indigestion, as she knew that during her periods in hospital, while on holiday, and occasionally at other times when she stopped taking the powders she did not have indigestion.

She lived alone on her earnings as a cleaner, her husband having died early in her married life, leaving her childless. She was much happier in hospital than she was at home and had little to gain in having her dyspepsia cured. The laparotomy had

In view of the above rather surprising findings a similar procedure was adopted in all cases of perforated peptic ulcer admitted to the surgical unit in this hospital within the period October, 1953, to October, 1954. Forty-four patients were questioned—31 with duodenal perforation, 12 with gastric perforation, and one with stomal ulcer perforation. Recently admitted patients of a similar age group were also questioned for control purposes. Only one patient admitted taking aspirin within six hours of acute duodenal perforation. A positive aspirin history was found in none of the control group.

Discussion

It is evident that aspirin may act as a severe gastric irritant in some people. This is particularly true of patients with peptic ulcer, one-third of whom are intolerant in varying degree to aspirin. The basic lesion produced by aspirin in such circumstances is an acute erosive gastritis, sometimes of surprising severity. In favourable circumstances—that is, the combination of a poor mucous reaction and the retention of relatively large portions of insoluble aspirin in the stomach—the lesion produced may be acute peptic ulceration, as was demonstrated in one specimen.

If we accept Forssell's (1938) hypothesis on the action of the muscularis mucosa—that is, a gripping action on solid particles, causing them to become imbedded in the mucosa—it is not surprising that an irritant insoluble particle gripped in this way for a sufficient length of time may result in the production of a lesion similar if not identical to an acute peptic ulcer. In the group of patients who received a particularly hard brand of aspirin—that is, one which did not readily break down into fine particles in contact with a solution—the effect on the mucosa was probably mitigated by the fortuitous selection of people who showed a good protective mucous reaction. The absence of really significant signs of gastric irritation with soluble calcium aspirin is to be expected from clinical impressions of its bland nature.

Approximately one-third of a group of peptic ulcer patients whose histories were such that the possible aetiological factors for their current exacerbation of symptoms could be reasonably assessed, admitted to taking aspirin within 24 hours of their breakdown. Such an assessment is obviously fraught with difficulties, since even well-recognized damaging factors such as emotional tension, exposure to cold, irregular meals, etc., are often multiple. It was felt, however, that histories such as those recorded (Cases 1 and 2) admitted of no other interpretation, and, although these were particularly striking examples, 14 others were in a similar vein. The other 17 patients who admitted to taking aspirin immediately before the exacerbation of their ulcer symptoms gave no previous history of aspirin intolerance.

Chronic dyspepsia from the frequent taking of aspirin is not uncommon, and clinicians should remember that gastric haemorrhage does not necessarily negative this diagnosis. In our experience the majority of such patients were middle-aged women of neurotic disposition, chronic swallowers of headache powders in surprising numbers—a fact which they usually concealed to the bitter end. Most of them suspected the cause of their dyspepsia, but were either unable to give up the habit or derived some cogent benefit from it.

The most surprising result of this investigation was, of course, the large number of people who admitted taking aspirin within a few hours of their haematemesis. It must be stressed that this fact was never volunteered by the patient. The taking of aspirin has become so commonplace that it is admitted only if asked for directly.

Even if the 11 patients of this series who took aspirin regularly are completely eliminated, there still remain 43 patients out of a total of 166 in whom aspirin was strongly indicated as at least a precipitating factor in their haematemesis. Furthermore, if the second group—those patients who took aspirin relatively frequently—is also eliminated, and the fact that they each gave a history of aspirin intolerance is ignored, 21 patients still remain in whom, in our opinion, aspirin was undoubtedly the major factor in precipitating their haematemesis—that is, approximately 1 in every 8 haematemesis patients in this series.

Nine of these patients gave no previous history of dyspepsia—that is, one-fifth of the acute lesion group in this series. It is this type of aspirin haematemesis which has been published in the past as an interesting rarity—for example, Richmond (1950). Our finding suggests that it is not such a rarity as many people believe, and that it is a rela-

tively common cause of gastric bleeding where there is no previous history of peptic ulceration.

Even in the presence of known peptic ulceration we believe that aspirin may be the precipitating cause of haematemesis, as it occurred in 12 patients at least in this series. This does not include a small group of 5 patients—of which Case 1 is a typical example—in whom a history indicated the likelihood of aspirin causing an exacerbation of ulcer symptoms eventually culminating in a haematemesis.

It is known that almost all patients with peptic ulcer have concomitant chronic gastritis of varying severity. It is not surprising, therefore, that a gastric irritant like aspirin exerts a maximum effect in ulcer patients, as we have shown from a study of their histories.

It is difficult to assess the site of a haemorrhage in this group—whether the bleeding is from an acute erosive gastritis induced by aspirin or from a chronic ulcer activated by it. We are of the opinion that bleeding was principally from a superimposed acute erosive gastritis, for the following reasons. Firstly, no presumed aspirin haematemesis was severe in this series. Of the 43 patients in this group only 3 required blood transfusion, the remainder responding rapidly to rest in bed, bland diet, sedatives, and alkali therapy (Cases 3, 4, 5, 6, and 7). If the bleeding had come from the chronic peptic ulcer known to be present in these patients, one would have expected at least a few to be more severe, although in so small a series no definite conclusion is possible. Secondly, the histories had a striking similarity, whether or not the patient suffered from peptic ulcer. Following aspirin, a variable latent period gave place to a bout of severe heartburn, culminating in the vomiting of blood, usually in small quantities, sometimes repeated, often fresh but occasionally altered.

For these reasons we had the tentative impression that aspirin haematemesis was, in the majority of patients, based on an acute erosive gastritis, whether or not peptic ulceration was also present. We found no evidence of defective blood coagulation or prothrombin content in any patient examined, thus excluding a salicylate-induced haemorrhagic diathesis as a contributory cause of the gastric bleeding.

The fact that aspirin did not play any possible part in an admittedly small series of peptic ulcer perforations also supported the gastritic origin of aspirin haematemesis. On the other hand, this finding is at variance with the clinical fact that aspirin may indeed cause an exacerbation of ulcer symptoms, as was previously shown.

In conclusion it is suggested that aspirin should never be given to patients with peptic ulceration, or indeed to those who have any gastric intolerance to it, however mild. Such an instruction should be given a prominent place in peptic ulcer advice charts, usually in place of much that could be safely left out. Some of these patients took aspirin on a full stomach only in powder form, with serious results, and, although this method almost certainly mitigates its irritant effects, it does not guarantee immunity. Calcium aspirin does not have this irritant action unless it has deteriorated through standing, and it can be used with impunity, especially if prescribed in soluble form. This simple measure would, in our opinion, cut down significantly the incidence of haematemesis and exacerbations of ulcer symptoms.

In a letter, Sir Arthur Hurst (1943) stated his belief that aspirin was the major cause of haematemesis in one-third of all cases in which peptic ulcer, gastric cancer, and cirrhosis of the liver could be excluded. He also estimated that aspirin haematemesis constituted 15 to 20% of all cases. The investigations here described support such an estimate, but a much larger series, preferably with selective gastroscopy, will be necessary to give a true indication of its frequency.

Summary

Aspirin is a serious gastric irritant, particularly in peptic ulcer patients.

It plays a significant part in exacerbation of ulcer symptoms and is at least a contributory cause in one in eight cases of haematemesis, and in one in five of that group with no major dyspeptic history.

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ACCIDENTAL HAEMORRHAGE

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During the past six years we have developed and maintained a special interest in accidental haemorrhage. In these years there have been 52,000 deliveries in the services of our two hospitals. Our investigations have included a study of the records of over 3,000 cases of accidental haemorrhage (including the necropsy findings in 100 cases) which were treated in the three Dublin Maternity Hospitals (Coombe, National Maternity, and Rotunda) over the period of 25 years from 1929 to 1953 inclusive.

A careful study of the case reports and statistics from Dublin and from other centres indicates that three complications render accidental haemorrhage one of the most serious happenings in present-day obstetrics. These complications are: (a) progressive and at times intractable haemorrhage, resulting from a deficiency in the clotting power of the blood; many of the hitherto imperfectly explained features of accidental haemorrhage are the natural results of this clotting defect; (b) anuric renal failure; and (c) foetal asphyxia. The foetal loss in all cases of accidental haemorrhage has been about 50%.

Deficiency in Clotting Power

We emphasize that the bleeding in a severe case of accidental haemorrhage is of a very special type. It is due to a fall in the level of the blood fibrinogen. Schneider has advanced an ingenious explanation of this occurrence. He has pointed out that the thromboplastin content of the decidua and placenta is very much higher than in most other tissues. When the placenta separates accidentally, the

disparity in the diameters of the arterial sinusoids of the endometrium and those of the retroplacental haematoma is such as to lead to an expanding force, activated in a manner comparable to that of a hydraulic pump. The pressure within the haematoma becomes very great and, bursting, its admixed tissue and decidual juices are forced into the intervillous lake. The liberation of thromboplastin in this way initiates coagulation. Thrombin is produced and the circulating fibrinogen is thereupon converted into fibrin. In our opinion, most of the fibrin formed in this way is deposited in the great vascular bed of the pregnant uterus.

At a certain level of falling blood fibrinogen (200 mg. per 100 ml.) haemorrhages are likely to occur. Liver replacement, which may take from 12 to 24 hours, fails to keep pace with fibrinogen conversion, so that hypofibrinogenemia results, with the onset of widespread haemorrhages, occurring spontaneously or induced by trauma. The uterus is not paralysed and incapable of contracting, but clotting power is lost. In spite of massage, oxytocic substances, contraction and retraction, blood transfusion, uterine plugs, and hysterectomy, haemorrhage continues from every traumatized point in the genital tract until death occurs or the clotting defect is corrected. If blood should lose its clotting power after premature separation of the placenta, more and more blood is poured out behind the detached placenta to overstretch the uterus. Shock is thereby induced from simple blood loss and from distension of the organ. The non-clotting blood can infiltrate between the uterine muscle fibres and escape into the broad ligaments and into and behind the peritoneal cavity. Thus there is still more shock from further blood loss and from tissue trauma and haematoma formation. The Couvelaire uterus might well be described as a diffuse haematoma of the uterus.

Once the maternal blood escapes without clotting, each tiny vascular breach will open wider, because it is not sealed off in the ordinary way. The stage is thereby set for the well-known clinical features of severe accidental haemorrhage: the tense, tender, Couvelaire uterus; the retroplacental and intraligamentous collections of blood; the haemorrhages under the capsule of the liver; the death undelivered; the death from intractable post-partum haemorrhage in spite of exploration, plugging, replugging, or hysterectomy; the death following caesarean section or caesarean hysterectomy. We believe that there is no unusual element of shock in these disasters. The patient dies from haemorrhage which is occurring not only from her genital tract, but into and about her abdominal organs, especially at the site of trauma, no matter how slight. The major loss may not be external. The condition is directly due to fibrinogenopenia, resulting from the absorption into the circulation of thromboplastin.

This clotting defect is to be found in the majority if not in all cases of combined and concealed accidental haemorrhage. Once it develops, bleeding must continue until the clotting power of the blood has been restored to normal. Serious loss of blood from the circulation is a constant feature of these cases. In a recent letter (to J. K. F.) Fletcher Shaw wrote: "I believe that hypofibrinogenemia gives me the answer, which I have so long desired, to a remarkable series of 11 cases of accidental haemorrhage treated 40 years ago by Clifford and myself in St. Mary's Hospital, Manchester. In all cases the uterus was markedly discoloured. One or both broad ligaments contained large effusions of blood which extended upwards to the lower pole of the kidney in two instances. One uterus showed minute cracks exuding blood like the splitting of a ripe plum. The pelves were filled by liquid blood. I can still visualize the dreadful picture as clearly as when I opened the abdomen. Five of the 11 cases survived caesarean hysterectomy. I came to the conclusion that the poor nutrition of wartime was a factor." Malnutrition and anaemia are indeed important associated conditions.

Since the amount of blood-coagulation substances in transfused fresh or citrated blood is relatively small (each pint of transfused blood has a fibrinogen content of about