1,000 µg of cyanocobalamin and a 24-hour collection of urine. A plasma sample was taken 10 to 12 hours after the oral dose of vitamin B₁₂. Radioactivity was measured in both an aliquot of urine and the plasma sample. If the results by these two methods did not agree, suggesting incomplete urine collection, the result of the urine test was rejected and the test repeated.

Results

The results are shown in the Table. There was no significant difference in the urinary excretion of vitamin B₁₂ between the

Results of Vitamin-B₁₂ Absorption Tests (Urinary Excretion; Schilling Test). Percentage of Oral 1-µg Dose of ⁵⁷Co-Vitamin B₁₂ in Urine

	No.	Schilling Test	
		Mean	Range
Controls	35	19.2	11.2-32.0
Pernicious anaemia (with 20 mg hog intrinsic factor)	29	12.8	3.8-23.0
Intrinsic-factor antibody			
In serum In gastric juice			
+	6	19.3	15.8-23.0
-	6	14.4	10.3-19.0
+	10	11.1	8.5-15.0
+	7	8.4	3.8-13.4

control subjects, the pernicious anaemia group without demonstrable antibody, and the pernicious anaemia group with only serum antibody. On the other hand, the group with antibody in gastric juice excreted (and hence absorbed) significantly less vitamin B₁₂ than did those pernicious anaemia patients without antibody ($P=0.01$), and this was even more so when the group with antibody in both serum and gastric juice was considered.

Discussion

Though it has been accepted that under special circumstances antibody to intrinsic factor will interfere with vitamin-B₁₂ absorption, the data presented here indicate that in pernicious anaemia this is the rule rather than the exception. The most pronounced effect was found in the "best antibody formers"—that is, those who had antibody in both serum and gastric juice. The data also indicate that the presence of antibody is an important factor in producing the severe degree of malabsorption of vitamin B₁₂ that leads to severe vitamin-B₁₂ deficiency. Thus the appearance of an intrinsic-factor antibody is able to convert a moderate degree of vitamin-B₁₂ malabsorption that does not necessarily lead to vitamin-B₁₂ deficiency (as in many cases of atrophic gastritis) to the relatively severe malabsorption found in pernicious anaemia.

On the other hand, the data confirm previous observations that serum antibody alone is less significant and where the antibody is confined to the serum compartment may have no effect at all on vitamin-B₁₂ absorption (Rose, Chanarin, Doniach, Brostoff, and Ardeman, 1970).

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Factors Predisposing to Recurrent Haemorrhage after Acute Gastrointestinal Bleeding*

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Summary

A retrospective survey of 472 consecutive hospital admissions for acute upper gastrointestinal bleeding showed that patients with a large initial bleed are more likely to bleed again than those with a small initial bleed. The incidence of recurrent haemorrhage is also related to the interval since the last bleeding episode, so that patients showing no clinical evidence of haemorrhage for 48 hours are unlikely to bleed again in the near future. Patients admitted after a haematemesis have a higher incidence of recurrent haemorrhage than those admitted after melaena only. Aetiology has been confirmed as an additional important factor, the incidence being highest in those with oesophageal varices or a chronic gastric ulcer. Contrary to widespread belief, age does not appear to affect the incidence of recurrent haemorrhage, nor do other constitutional factors such as sex or the ABO blood group.

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Introduction

Recurrent haemorrhage after admission to hospital results in a twelvefold increase in medical mortality rate (Avery Jones, 1956) and is therefore generally regarded as the main indication for emergency surgery. Unfortunately, a policy of selective emergency surgery in these patients has failed to reduce the overall mortality rate significantly (Avery Jones, 1956; Schiller *et al.*, 1970). An improvement in mortality rate seems more likely to result from a policy of operating on patients before, rather than after, they rebleed, so that a method of recognizing patients at special risk of recurrent haemorrhage might have important therapeutic implications. Apart from the observation that patients with a chronic gastric ulcer are at an increased risk (Avery Jones, 1956), very little is known about factors predisposing to recurrent haemorrhage.

Methods

Careful records are kept in the gastroenterology department of all patients admitted to the Central Middlesex Hospital with acute gastrointestinal bleeding. Almost all these patients are admitted to one of the two gastroenterology wards. This system offers considerable advantages for retrospective analysis,

since complete records are available and there is a uniform policy of management. A retrospective study has been made of the records of all patients admitted during the three-year period 1962-4. The information obtained from these records has been analysed by means of a punch-card system. In analysing factors affecting the incidence of recurrent haemorrhage, only those patients having a definite rebleed following admission, as shown by a haematemesis, have been classed as rebleeders.

Results

A total of 472 patients were admitted during the three-year period 1962-4. Of these, 82 (17.5%) had a haematemesis after admission and have been classed as rebleeders.

Aetiology.—Rebleeding occurred in 7 out of 10 patients with oesophageal varices (70%), in 21 out of 67 with a chronic gastric ulcer (32%), in 22 out of 179 with a chronic duodenal ulcer (12%), in 15 out of 106 in whom a barium meal examination showed some other lesion (14%), and in 17 out of 110 in whom the barium meal examination was normal (15%). The last three groups showed no significant difference in the incidence of rebleeding, and have therefore been merged as a single group of "other aetiologies," with an overall incidence of 14%. The difference in incidence between those with oesophageal varices and those with "other aetiologies" is unlikely to be due to chance ($P < 0.0005$), as is the difference between those with a chronic gastric ulcer and those with "other aetiologies" ($P < 0.0005$), and between those with oesophageal varices and those with a chronic gastric ulcer ($P < 0.05$). The fact that aetiology influences the incidence of rebleeding makes it necessary, in analysing the effect of other factors, to take account of the proportion of each subgroup with different aetiologies. The incidence of rebleeding has therefore been standardized for aetiology according to the three subgroups (oesophageal varices, chronic gastric ulcer, and "other aetiologies"). The value of χ^2 has been obtained by calculating separately the expected number of patients who rebled for each aetiology within each subgroup and averaging the result.

Age.—Of the 258 patients aged 60 or more, 43 rebled, and of the 214 aged less than 60 years, 39 rebled. The standardized incidence of rebleeding (18%) was the same in both groups ($0.98 < P < 0.99$).

Sex.—Of the 294 males 45 rebled, and of 178 females 37 rebled. The standardized incidence of rebleeding in the males (16%) was not significantly different from that in the females (20%; $0.8 < P < 0.9$).

ABO Blood Group.—Thirty out of 209 patients of blood group O rebled, as did 52 out of 263 patients of other blood groups, giving a standardized incidence of 14% and 21% respectively ($0.1 < P < 0.2$). There was no significant difference in incidence between blood groups A, B, and AB.

Type of Preadmission Bleed.—Of 323 patients admitted following a haematemesis 77 rebled (23%), whereas of 148 admitted following melaena only, 5 rebled (4%; $P < 0.0005$).

Severity of Initial Bleed.—In patients admitted three or more days after their initial bleed the haemoglobin level on admission is an indication of the severity of the bleed, since haemodilution has had time to occur. Of 75 patients admitted at this time interval with a haemoglobin level of less than 9 g/100 ml, 10 rebled (15%), whereas of 37 patients admitted with a haemoglobin level of more than 9 g/100 ml, none rebled ($P < 0.05$).

Time Interval since Last Preadmission Bleed.—Of 379 patients who gave a history indicating a fresh bleeding episode within two days before admission, 79 (20%) rebled, whereas only 3 of the 93 patients (3%) not giving this history rebled ($P < 0.001$).

Timing of First Rebleed after Admission.—Of the 82 patients having a definite rebleed, the day of the rebleed was

recorded in 80. In 75 the first rebleed occurred within the first two days following admission, giving an incidence within this time interval of 16%. Of the remainder, four had a definite rebleed on the third to fifth days (1%), and only one, with oesophageal varices and hepatic coma, had his first rebleeding episode later than the fifth day (0.2%). In those who had not already rebled, the tendency for the incidence of rebleeding to diminish with the passage of time is unlikely to be due to chance ($P < 0.0005$).

Discussion

The present study has confirmed that patients with a chronic gastric ulcer have a high incidence of recurrent haemorrhage (Avery Jones, 1956), and has also shown that the incidence is even higher in those with oesophageal varices. The incidence in those with a chronic duodenal ulcer, on the other hand, does not appear to differ from that found in those with a normal barium meal examination.

Age has a big influence on prognosis in acute gastrointestinal bleeding (Avery Jones, 1943, 1947 and 1956; Fraenkel and Truelove, 1955), the age of 60 being the critical point (Avery Jones, 1956). This increase in mortality rate is usually attributed to an increase in the incidence of recurrent haemorrhage, on the ground that atheroma in older patients may prevent a bleeding artery from constricting sufficiently to stop the haemorrhage (MacLean, 1962; Avery Jones *et al.*, 1968). My findings do not support this view, since the incidence of rebleeding was the same in those aged less than 60 as in those aged 60 or over. The increase in mortality rate in those aged 60 or over is presumably the result, not of an increased incidence of rebleeding but of a diminished ability to withstand the stress of rebleeding if it does occur.

Another constitutional factor that has been studied is the ABO blood group system, since patients with blood group O have been found to have an increased liability to gastrointestinal bleeding (Langman and Doll, 1965). In the present study patients of blood group O did not have an increased liability to recurrent haemorrhage after admission.

Patients in whom the initial bleed occurred three or more days before admission had a significantly higher incidence of rebleeding if their haemoglobin level on admission was less than 9 g/100 ml. In these patients there had been ample time for haemodilution to occur, so that this finding suggests that patients with a severe initial bleed are more likely to rebleed than those with a mild initial bleed. This view is supported by the finding that patients admitted after a haematemesis had a higher incidence of rebleeding than those admitted after melaena only, since a prospective study has shown that a haematemesis indicates a large haemorrhage (Northfield, 1970).

These findings provide objective evidence to support the suggestion of Tanner (1950) that any patient aged over 45 with severe bleeding and a known history of chronic ulcer should be operated on as soon as he is resuscitated. The problem here is to recognize which patients have had a severe bleed; blood volume and red cell volume studies (Tibbs, 1956; Tudhope, 1958) have shown the limitations of measurement of pulse rate, blood pressure, and haemoglobin level for this purpose in patients admitted soon after the initial haemorrhage. On the other hand, central venous pressure measurements are valuable in assessing the severity of the initial bleed and thereby identifying a group of patients at very high risk of recurrent haemorrhage (Northfield and Smith, 1967, 1970).

The present study has shown the effect of time on the incidence of recurrent haemorrhage. Whereas the incidence of rebleeding after admission was 20% in those who had had a definite bleed within two days before admission, it was only 3% in the remainder. The same effect was seen after admission, since 94% of patients having a definite rebleed had the

first rebleed within the first two days following admission. It therefore seems that a lesion that has not bled for two days is unlikely to bleed again in the near future.

This finding raises the possibility of limiting the period of stay in hospital of patients with acute gastrointestinal bleeding. At present this period is commonly two to three weeks even in those not requiring emergency surgery. In the present study only one patient during a three-year period rebled for the first time later than the fifth day after admission, and in this case the haemorrhage was a terminal event in a subject admitted in hepatic coma, so that there could not have been any question of an early discharge from hospital. These findings suggest that no risk would be entailed by discharging from the sixth day onwards patients who have not shown any evidence of rebleeding, so long as there is no other indication for keeping them in hospital.

It is often difficult to decide whether to admit a patient who has been passing melaena stools for several days, is feeling well, and is not anaemic. The present investigation suggests that this is not necessary, since no patient admitted three or more days after the initial bleed with a haemoglobin level of more than 9 g/100 ml subsequently rebled.

A method of selecting patients for emergency investigation by barium meal examination or gastroscopy is needed (Truelove and Reynell, 1963), since such investigation of all

patients throws an unnecessary burden on the x-ray department, with the necessity in some cases of cancelling routine booked examinations. In this context it is worth noting that patients admitted after a haematemesis are at considerably greater risk of recurrent haemorrhage than those admitted after melaena only.

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PRELIMINARY COMMUNICATIONS

Induction of Therapeutic Abortion by Intra-amniotic Injection of Urea

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Summary

A new method of mid-trimester termination of pregnancy is described in which intra-amniotic urea was used. The mean interval between intra-amniotic injection and abortion was 59 hours and the mean length of hospital stay six days; the fetomaternal haemorrhage incidence was one out of 10 cases, which compares favourably with other methods. No complications have yet been encountered.

Introduction

The increasing demand for termination of pregnancy has inevitably led to delay in appointments for gynaecological outpatient clinics and admission to hospital. Because of this more patients need their pregnancy terminated in the mid-trimester, when a vaginal procedure may be very hazardous. In our view hysterotomy is the method of choice whenever sterilization is to accompany termination. We believe, however, that the inevitable uterine damage and possible weakness should be avoided when future child-bearing is a possibility.

Intrauterine injections, via the cervix, of soapy pastes of the Aretus/Utus type have been used since the 1930s, and Barns (1947) enthusiastically reported a success rate of 80% with a specially prepared soap paste in a series of 71 patients. Complications were limited to mild pyrexia and blood loss in only a few cases. Use of Utus paste was favourably described by Lachelin and Burgess (1968), who were successful in all of the 182 cases, and only 13 (7%) developed a pyrexia requiring antibiotics. We have abandoned this method, however, after five severe pelvic infections in the last 20 terminations, two of which developed *Escherichia coli* septicaemia.

Amniocentesis and the injection of 50% dextrose has been used with great success by Brosset (1958) and Lewis *et al.* (1969), but there remains the potential hazard of intrauterine infection and the possibility of thromboembolic complications if, in error, part of the injection is made intravenously.

The injection of 20% hypertonic saline has been more widely used than glucose (Turnbull and Anderson, 1965; Csapo, 1966-7; Menzies and Hawkins, 1968). The method is both effective and convenient, but maternal deaths have occurred, and Wagatsuma (1965) reported 25 deaths in Japan between 1946 and 1952. It may be significant that most of the deaths were associated with 30% saline rather than the 20% concentration. Cameron and Dayan (1966) also reported two deaths—one patient had been given a general anaesthetic, and in the other case twice as much hypertonic saline had been injected as liquor aspirated. Post-mortem findings showed acute haemorrhagic infarction of the amygdaloid nucleus and adjacent structures and also a Y-shaped infarct in the pons, thought to be due to excessive cerebral dehydration following inadvertent intravenous or intraperitoneal injection of 20% saline.

Study of these reports suggests that failures of technique may have been a main feature of the hypertonic saline deaths. In considering alternatives to saline on theoretical grounds urea seemed the safest possible substance, and we decided to try the induction of abortion with intra-amniotic

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