Gastric Ulcer: *

Classification, Blood Group Characteristics, Secretion Patterns and Pathogenesis

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FOR MANY YEARS ulcers of the stomach and duodenum were classified as a single disease. As a result some of their differing features cancelled out and were concealed in consideration of peptic ulcer as a whole. They are now generally recognized as distinct entities, and considered by many to have different pathogeneses.

Dragstedt's theory that duodenal ulcers are caused by neurogenic acid hypersecretion, and gastric ulcers by acid hypersecretion of hormonal origin, ignores the fact that less than 50 per cent of gastric ulcer subjects are acid hypersecretors. Vanzant *et al.*[16] and many others, demonstrated that, on the average, gastric ulcer subjects produce less hydrochloric acid in response to a meal than do normal people.

It has also been suggested that duodenal ulcers are the result of over-powerful acid attack and gastric ulcers of a breakdown in defence. I have remarked[9] that hyposecretion of acid is associated with diminished production of mucus, but the fact that gastric ulcer sometimes occurs in a hypersecretor needs further explanation.

It is held that these difficulties are due to the anatomic division of ulcers according to their relation to the pylorus. They are resolved when a more appropriate, physiologic division is adopted, based on acid secretion level.

The acid secretion of patients with gastric ulcers greatly varies. Although most are hyposecretors, two kinds are usually moderate, and sometimes gross hypersecretors. These are patients with gastric ulcers which are combined with duodenal ulcers, and those with ulcers on or near the pylorus. Gastric ulcers distant from the pylorus and without preceding duodenal lesions, which are the more frequently occurring, are found much more constantly to be associated with hyposecretion.

Combined Gastric and Duodenal Ulcers

In an analysis of 130 cases of combined gastric and duodenal ulcer I reported[7, 8] that:

1) The duodenal ulcer was the first to appear.

2) The associated mean secretion pattern was between that characteristic of duodenal ulcer and of established pyloric obstruction. Most patients had a level of acid secretion typical of duodenal ulcer alone and quite different from that of most gastric ulcers.

3) A majority of patients had evidence of gastric retention, and many had obvious pyloric obstruction.

4) Gastric ulcers combined with duodenal ulcers were particularly resistant to medical treatment and bled more frequently than other gastric ulcers.

In a subsequent report,[11] on patients with emergency hemorrhage, the proportion who had combined ulcers was relatively high, and it was usually the gastric ulcer which bled. It seemed that ulcers of

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this type could be secondary to gastric retention. Prolonging of the hormonal phase of acid secretion could contribute to their pathogeneses. However acid hypersecretion also probably preceded the duodenal ulcer and the retention.

Gastric Ulcers and Blood Groups

Periodically peptic ulcer has been associated with blood group O, and in 1954 Aird, Bentall, Mehigan and Roberts[1] put this observation on a sound statistical basis. These authors remarked that their duodenal ulcer patients showed a more striking preponderance of group O than did those with gastric ulcers. However, as the difference was not statistically significant they did not feel justified in separating them for the purpose of analysis. However, the difference has since been confirmed by many centers.

On the basis of an international study Roberts[14] reported that a person of blood group O had a chance of developing a duodenal ulcer 38 per cent greater than had a person of another group; on the other hand he had a chance only 19 per cent greater of developing a gastric ulcer.

Holding that gastric ulcers were often secondary to duodenal ulcers, and that prepyloric and pyloric ulcers more resembled duodenal than primary gastric ulcers, I suggested that these two kinds of gastric ulcer might be associated with the same blood group O preponderance as were duodenal ulcers. They alone would then account for the whole of the smaller group O preponderance seen in gastric ulcers collectively.

An analysis of 523 patients with gastric ulcer,[10] indeed showed the expected result. In this series ulcers distant from the pylorus and without preceding duodenal or pyloric lesions were associated with a small, group A excess. However, these data only just achieved statistical significance at the conventional 1 in 20 level and required confirmation by larger numbers. Accordingly a series of 5,023 cases is now reported.

Three Types of Gastric Ulcer

Type 1. This is an ulcer in the body of the stomach without abnormality of the duodenum, pylorus or prepyloric region. In the pilot survey patients with these lesions had a low level of acid secretion and a small blood group A preponderance. Their pain was usually relieved by lying down and was rarely experienced at night. Hemorrhage was less common than in other types, and the prognosis was relatively good.

Category 1a. During operation for gastric ulcer, meticulous examination of the duodenum, pylorus and prepyloric region revealed small lesions or their scars more frequently than had been expected.

Since more casual inspection would result in Type 2 or secondary lesions being classified as Type 1, only those cases in which the operation notes specifically referred to the duodenum and pylorus, and described them as normal, were admitted. All other apparent Type 1 cases were put into a separate Category 1a for consideration only with the series as a whole.

Type 2. This is an ulcer in the body of the stomach combined with, and probably secondary to, an ulcer or its scar in the duodenum or at the pylorus. Although patients with ulcers of this type usually exhibit well-marked or even gross acid hypersecretion, in many the rate of secretion is low. Sometimes there is a known history of duodenal ulceration or perforation, or clinical evidence of pyloric obstruction with a tendency to evening vomiting. Night pain has usually been experienced, though it may have subsided since the onset of gastric retention with its more complete intragastric buffering of acid ions. These ulcers have a bad prognosis. They are very resistant to medical treatment and have a

strong tendency to bleed. It is my practice to recommend surgical treatment for ulcers of Type 2 unless there are strong contraindications.

Type 3. This is a gastric ulcer close to the pylorus. Lesions in this position which were combined with duodenal ulcers, or with a Type 2 ulcer proximal to them, were all classified as Type 3.

Patients with prepyloric gastric ulcers, like those with duodenal ulcers, usually have acid hypersecretion and in the pilot survey exhibited a similar blood group O excess.

It has not proved practicable to classify a Type 3 ulcer as one occurring within a specified distance of the pylorus. Instead, it has been necessary to rely on the appearances at operation. It has been described as an ulcer to the right of the gastric angulus (the lowest point of the lesser curve).

Controls

(Table 4.) In Great Britain there exists a very large blood-donor panel, and the consecutively registered blood donors in the immediate vicinity of each hospital contributing to the survey have been used as controls. In London, all the series have been compared with the same set of controls, those of Kopeć[12] for a western part of London from which all the patients came. This has not been equally representative for all areas, for the population varies considerably from place to place with respect to ethnic groups. This is particularly true in the distribution of the Irish, a people who have a considerably larger proportion of blood group O than do the English.

Results of Blood Group Studies

The Series as a Whole (Tables 1–3). There were 5,023 cases of gastric ulcer in the whole series. Of these 2,885 (57%) were assigned to Type 1 or Category 1a, 1,126 (22%) to Type 2 and 1,016 (20%) to Type 3. Of the Type 1 ulcer patients 880 were put in Category 1a, which undoubtedly also contained a number of unidentified Type 2 cases.

The apparent incidence of gastric ulcers of all types together in persons of group O relative to that in others was 1.22, which is within 3 per cent of that calculated from the combination of many areas by Fraser Roberts.[14] The preponderance of blood group O among patients with gastric ulcer, as with duodenal ulcer, varied substantially from place to place, showing a high χ^2 value for heterogeneity. This may have been partly due to variations in the controls.

The apparent incidences of ulcers according to types in persons with blood of different groups, were compared by the method of Woolf.[18]

Type 1. The 2,001 Type 1 ulcer patients showed a significant preponderance of blood group A and diminished frequency of all other groups. The mean weighted incidence of Type 1 ulcers in persons of blood group A relative to that in those having blood of other groups was 1.16. The value for χ^2 was 10.0 for one degree of freedom, indicating a chance of fortuity of less than 1 per cent. However χ^2 for heterogeneity was 22.9 for ten degrees of freedom, which is too high to be attributable to chance. This must be judged to indicate real geographic variation in the coefficient of correlation between the incidences of Type 1 ulcer and blood groups.

Types 2 and 3. Patients with ulcers of Types 2 or 3 showed a very substantial correlation with group O, the apparent incidence in persons of blood group O relative to that of other groups being 1.45 and 1.58, respectively. This incidence is higher than any reported for duodenal ulcer and much

TABLE 1. *Numbers of Patients from Each Center with Each Type of Ulcer**

	O	A	B	AB	Totals	%
Hospital A: London						
Type 1	126	136	28	8	298	57
Category 1a	89	69	11	4	173	
Type 2	105	74	10	6	195	24
Type 3	91	51	12	2	156	19
Totals	411	330	61	20	822	
Hospital B: London						
Type 1	113	123	19	7	262	61
Category 1a	17	6	—	1	24	
Type 2	38	45	8	2	93	20
Type 3	49	30	10	0	89	19
Totals	217	204	37	10	468	
Hospital C: London						
Type 1	61	85	22	7	175	69
Category 1a	64	62	10	3	139	
Type 2	47	32	2	3	84	18
Type 3	26	22	6	1	55	13
Totals	198	201	40	14	453	
Hospital D: London						
Type 1	28	19	2	—	49	60
Category 1a	12	16	1	—	29	
Type 2	7	4	2	—	13	10
Type 3	31	8	1	—	40	30
Totals	78	47	6	—	131	
Hospital E: London						
Type 1	175	126	28	12	341	65
Category 1a	99	83	20	7	209	
Type 2	52	42	10	3	107	13
Type 3	82	81	18	6	187	22
Totals	408	332	76	28	844	
Hospital F: London						
Type 1	67	71	7	4	149	46
Category 1a	27	18	5	0	50	
Type 2	73	35	6	3	117	27
Type 3	74	34	6	2	116	27
Totals	241	158	24	9	432	
Hospital G: London						
Type 1	51	35	17	1	104	53
Category 1a	97	74	11	4	186	
Type 2	85	60	7	6	158	29
Type 3	62	32	5	1	100	18
Totals	295	201	40	12	548	
Middlesbrough, N.E. England						
Type 1	101	99	14	3	217	49
Type 2	83	29	15	2	129	29
Type 3	61	30	4	1	96	22
Totals	245	158	33	6	442	

TABLE 1.—(*Continued*)

	O	A	B	AB	Totals	%
Bristol, S.W. England						
Type 1	95	82	5	7	189	57
Type 2	39	25	4	3	71	21
Type 3	35	30	6	2	73	22
Totals	169	137	15	12	333	
Belfast, N. Ireland						
Type 1	49	57	7	3	116	54
Category 1a	33	28	7	2	70	
Type 2	41	15	3	0	59	17
Type 3	75	18	7	2	102	29
Totals	198	118	24	7	347	
Preston, N.W. England						
Type 1	37	52	7	5	101	50
Type 2	42	12	4	0	58	29
Type 3	26	13	5	0	44	22
Totals	105	77	16	5	203	

* The right hand column gives the proportion of patients with ulcers of each type at each center.

TABLE 2. *Total Number of Patients in Whole Series with Each Type of Ulcer and Each ABO Blood Group*

	O	A	B	AB	Totals
Type 1 (strict)	903	885	156	57	2001
Category 1a	438	356	65	21	880
Type 2	632	389	75	30	1126
Type 3	592	333	76	15	1016
Totals	2565	1963	372	123	5023

TABLE 3. *Blood-Group Proportions for the Three Types of Ulcer and for the Series as a Whole. The Controls Have Been Weighted in Simple Proportion to the Number of Patients in Each Category from each Center**

%	O	A	B	AB	Relative Incidence: O to Non-O
Type 1	45.13	44.23	7.80	2.85	0.94
Controls for type 1	46.71	40.76	9.34	3.19	
Category 1a	49.77	40.45	7.39	2.39	1.11
Controls for category 1a	47.23	40.27	9.36	3.12	
Type 2	56.13	34.55	6.66	2.66	1.45
Controls for type 2	46.82	40.67	9.38	3.13	
Type 3	58.27	32.78	7.48	1.48	1.58
Controls for type 3	46.88	40.52	9.41	3.19	
Totals	51.07	39.08	7.41	2.45	1.22
Controls for whole series	46.49	40.87	9.43	3.21	

* The relative incidence of Type 1 ulcers, A to non-A, was 1.16.

TABLE 4. *Blood-Group Distribution of Blood-donor Controls. Percentages in Parenthesis*

	O	A	B	AB	Total
Postal Districts of W. London	9,173 (47.11)	7,898 (40.56)	1,798 (9.23)	604 (3.10)	19,473
Town of Middlesbrough	777 (46.31)	668 (39.81)	164 (9.77)	69 (4.11)	1,678
Postal District of Bristol	1,430 (43.54)	1,485 (45.22)	275 (8.37)	94 (2.86)	3,284
City of Belfast	5,522 (48.75)	4,192 (37.01)	1,229 (10.85)	384 (3.39)	11,327
Town of Preston	938 (45.51)	857 (41.58)	208 (10.09)	58 (2.81)	2,061

higher than the figure for all types together of gastric ulcer in this series (1.22). This positive correlation gave values for χ^2 of 36.3 and 44.8 for one degree of freedom, highly significant, indicating a chance of fortuity of only one in many thousand in each case. However, again the data were very heterogeneous, χ^2 for homogenity being 27.7 and 36.4 for ten and nine degrees of freedom, respectively. This could have been due to variations in representativeness of control populations, and in order to eliminate this particular source of error the relative incidence of ulcers of Type 1 was compared direct with that of Types 2 or 3. Again the correspondence was very striking and gave a value for χ^2 of 49.98 for one degree of freedom, but again there was marked heterogeneity ($\chi^2 = 49.24$ for 10 degrees of freedom). Another possible explanation could be difference in precision with which the various types of ulcer had been classified by different surgeons.

The blood group O correspondence among 215 patients whose ulcers were known to be on the borderline between Types 1 and 3, that is at the gastric angulus or the junction of the antrum and body of the stomach, lay between those characterizing Type 1 and Type 3 ulcers.

Acid Secretion Investigations

When gastric ulcers are classified as described, the average resting acid secretion pattern associated with Type 1 ulcers differs substantially from those of Type 2 or 3. This was suggested by the pilot survey[10] but can now be statistically evaluated.

All-night acid secretion studies were made on 153 patients classified by ulcer type. From each half, respectively, there was aspirated more than and less than 201 ml. of gastric juice. In the juice of one half there was more than, and in the other half less than, 15 mEq. of HCl/L. Among those with ulcers of Type 1, 49 of 70 secreted less than the overall mean volume, and in 45 of 63 the juice was below the mean level of acidity. In patients with ulcers of Types 2 or 3, 55 of 82 gave more than the mean volume, and 58 of 89 gave juice of more than the mean level of acidity (Tables 5 and 6).

These data give χ^2 values of 20.8 and 30.6, respectively, for one degree of freedom, only the remotest of chances that these results are fortuitous. They establish that there is a real and substantial difference in resting acid secretion rate between patients with Type 1 ulcers and those with ulcers of Type 2 or 3.

Pathogenesis of Gastric Ulcers

Hypersecretion Ulcers: Type 2 and 3. Gastric ulcers occurring as a complication of duodenal ulcers, and juxtapyloric gastric ulcers, both tend to occur—as do duodenal ulcers—in hypersecreting individuals, though the onset of pyloric obstruction often modifies these findings in late cases. However, though antral ulcers, like duodenal ulcers, may be caused by hypersecretion, other factors must be considered in ulcers of Type 2.

Gastric ulcers tend to complicate gastric retention, whatever its cause, even in the

TABLE 5. *Titratable "Free" Acidity of Bulked All-night Gastric Secretion in 153 Gastric Ulcer Patients (in mEq./L.)*

	0–	10–	20–	30–	40–	50–	60–	70–	80–	90–
Type 1	39	9	7	3	1	2	1	1	1	0
Types 2 or 3	17	16	9	9	10	15	6	4	1	2
Total	56	25	16	12	11	17	7	5	2	2

absence of acid hypersecretion. Gastric ulcers have been encountered after vagotomy when this operation was used alone. I have seen them proximal to antral carcinomas, and they were also observed subsequent to vagotomy in rabbits [4] and pyloric ligature in rats.[15] In all these instances gastric retention was present.

Since former duodenal ulceration is the most common cause of gastric retention (in Britain) it was expected that the majority of Type 2 ulcers would be associated with acid hypersecretion. However, it seems that the retention may be as important pathogenetically and could operate by prolonging the acid attack rather than by intensifying it.

Hyposecretion Ulcers: Type 1. Excessive hormonal stimulation may occur in the presence of gastric retention and may help to promote a gastric ulcer of Type 2 as a complication of a duodenal ulcer. I have also shown that prepyloric ulcers occur in patients whose acid secretion averages more than that of healthy people. The mean secretion rate for patients with gastric ulcers of any kind, however, is below normal, for this average has been influenced by the consistently low rate of acid secretion in patients with primary ulcers in the body of the stomach.

Several factors may promote ulcers in persons with acid hyposecretion: 1) associated hyposecretion of mucus, 2) prolonging of the acid attack when gastric retention is present and 3) local slowing of the already-critical rate of mucus secretion which must result when submucosal arteriovenous shunts are opened.

I have shown experimentally [9] that hydrogen ions penetrate gastric mucus at about 1 mm. per hour. But if the mucus is wiped off the stomach lining at operation it is replaced at a rate much faster than that required to produce a depth of 1 mm. in an hour, i.e., faster than it is acidified. This explains why Wolf and Wolff [17] found that the pH of the mucus lining the stomach never fell below 4, regardless of how strong the acid in contact with it.

However, cells which secrete cannot do so indefinitely without rest, and a sufficiently *prolonged* acid attack would overwhelm them. Wolf and Wolff also observed that diminished blood supply slowed the rate of mucus secretion, and this is the local effect of arteriovenous shunts opened in the gastric wall. Barlow [2] demonstrated that these shunts open under the influence of adrenalin.

TABLE 6. *Volume (ml.) of All-night Gastric Secretion in 153 Gastric Ulcer Patients*

	0–	100–	200–	300–	400–	500–	600–	700–	800–	900–	1,000+
Type 1	23	24	13	4	0	2	2	1	0	1	0
Types 2 or 3	5	21	11	12	7	8	3	5	5	1	5
Total	28	45	24	16	7	10	5	6	5	2	5

TABLE 7. *Duodenal Ulcer Patients Divided by Volume and by Acidity of Bulked All-night Secretion, and by Blood Groups**

	0–300 ml.	300–600 ml.	600–900 ml.	over 900 ml.	Controls
Group O	44 (64)	39 (71)	15 (71)	9 (82)	9,173 (54)
Group A	25 (36)	16 (29)	6 (29)	2 (18)	7,898 (46)
	0–30 mEq./L.	30–60 mEq./L.	60–90 mEq./L.	over 90 mEq./L.	Controls
Group O	32 (62)	40 (66)	30 (71)	9 (100)	9,173 (54)
Group A	20 (38)	21 (34)	12 (29)	0 (0)	7,898 (46)

* Figures in parenthesis = percentage of (O + A).

Discussion

Since blood type is an inherited characteristic, it follows that the association of any disease with a particular blood type implies an hereditary factor in pathogenesis.

Køster *et al.*[13] recalled that diseases such as pernicious anemia and carcinoma of the stomach more often affect patients with blood group A and those with an absence or low rate of acid secretion. Patients with diseases such as duodenal ulcer, and especially stomal ulcer,[5] predominantly have blood group O and usually have acid hypersecretion. They showed that the relationship had a high level of statistical significance. Among patients with gastric ulcers there is also a preponderance of blood group O in those with hypersecretion and of blood group A in those with hyposecretion.

Baron [8] reported a gradient of acid secretion rates with a *low* associated with ulcers in the body of the stomach and a *high* with those near the pylorus. This may be compared with the gradient observed in the coefficients of correlation between blood group O preponderance and distances of the ulcer proximal to the pylorus. Serum pepsinogen concentration is believed to afford a reasonable index of acid secreting potential, and Hanley [6] reported that normal persons with blood group O have higher mean levels of serum pepsinogen than do those with other blood groups.

In Table 7, duodenal ulcer patients are divided according to blood type and acid secretion rates. There is a strong suggested association between blood group O and the higher levels of both acidity and juice volume, though at all levels the proportion of duodenal ulcer patients with blood group O is well above average. On the basis of this small series, duodenal ulcer patients with blood group A secrete more acid than normal persons of any blood group.

These data suggest that a tendency towards acid hypersecretion is hereditary and that this, in turn, predisposes to duodenal or prepyloric ulceration.

A previous study [7] indicated that gastric ulcer when combined with duodenal ulcer is a late complication of the latter, and this suggested the possibility of a similar association with respect to blood groups. However the association of gastric ulcers of Type 2 with blood group O is even more marked than that of duodenal ulcer. The implication that ulceration of the stomach tends to develop particularly in the most severe cases of duodenal ulcer corresponds with clinical experience.

Studies with respect both to blood types and to acid secretion show that the classification of peptic ulcers into duodenal and gastric is unhelpful. Both prepyloric and combined ulcers have much more in common with duodenal ulcers than with those occurring as a primary lesion in the body of the stomach.

The suggested classification is particularly important in treatment. Just as duo-

denal and gastric ulcers are known to require different emphases in treatment, it should now be recognized that all gastric ulcers should not be managed alike. Hypersecretion when present should be treated whatever the location of the ulcer. No operation specific for control of either hypersecretion or hyposecretion should be adopted as a routine procedure for all gastric ulcers on an anatomic basis alone, without regard to ulcer type.

Summary

It has long been suspected that not all peptic ulcers are alike, and in recent years duodenal and gastric ulcers have been regarded as different diseases with possibly different pathogeneses. Results of this study indicate a physiologic basis for the classification of peptic ulcers. Gastric ulcers occuring with duodenal ulcers and those near the pylorus should be classified with duodenal ulcers as a disease of acid hypersecretion; those occurring in the body of the stomach in a patient with a normal duodenum are usually characterized by acid hyposecretion. They constitute a different disease with different pathogenesis and different hereditary predisposition.

It is proposed that peptic ulcers be classified not anatomically but rather on the basis of hypo- or hypersecretion. The importance of this concept in relation to treatment is stressed.

A hypothesis has been advanced for the pathogenesis of hyposecretion ulcers.

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