α_2^G with the normal δ_2 of Hb A₂. The abnormal minor component in our propositus (Q₂) could be explained along the same lines as a combination of α_2^Q and δ_2 —that is $\alpha_2^Q\delta_2$. Further support for this hypothesis is obtained from the observation that the father's haemoglobin contains both A₂ and another minor fraction corresponding to the child's Hb Q₂ (Fig. 6).

Summary and Conclusions

Hb Q- α -thalassaemia was found in a Thai infant. The father is an Hb-Q-trait carrier, and the mother has α -thalassaemia. An interesting feature in the child is the absence of Hb A₂ which is replaced by "Q₂"; in the father A₂ and Q₂ are present together. Taken together with a previously described case of "Hb Q-H disease" the present study establishes a new concept—Hb Q- α -thalassaemia.

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ABO BLOOD GROUPS OF SIBLINGS OF GASTRIC ULCER AND GASTRIC CARCINOMA PATIENTS*

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An increased frequency of blood group O has been found in gastric ulcer patients and an increased group A frequency in gastric carcinoma patients (Buckwalter *et al.*, 1956). Blood donors were used as controls for these studies. Inadvertently, blood donors may be selected from a different stratum of the population than the patients. Differences between the blood type frequencies of the controls and patients might, in this event, reflect anthropological differences between the two strata of the population rather than cause-and-effect association between the ABO blood groups and the

disease in question. By elimination of the possibility of population stratification the siblings of the patients should provide more reliable controls (Clarke *et al.*, 1956). The results of sibship studies support a cause-and-effect explanation for the association between the ABO blood groups and duodenal ulcer (Buckwalter *et al.*, 1960). This is a report of similar studies of siblings of patients with gastric ulcer and gastric carcinoma.

Methods.—The clinical material was provided by patients of the University of Iowa and Iowa City Veterans Administration Hospitals. The diagnosis was based on morphological findings in all of the gastric carcinoma patients and in two-thirds of the gastric ulcer patients; the remainder of the gastric ulcer patients had "ironclad" clinical diagnoses. The methods were the same as those used in the study of duodenal ulcer siblings. The same controls were used. In analysing gastric carcinoma sibships, A₁ and A₂ were regarded as "A" blood, while A₁B and A₂B were regarded as "non-A" blood. The sibships were also analysed after eliminating all sibs differing in sex from their propositi.

Results

The numbers and percentages of the propositi with gastric ulcer, their affected sibs, unaffected sibs, sibs whose ulcer status was unknown, and controls of each ABO blood group are recorded in Table I. Note the increase in group O frequency in propositi (I), as compared with controls (V). When the differences between the blood-type frequencies of the propositi and controls are tested for statistical significance by the chi-square method with three degrees of freedom, $0.02 < P < 0.05$. When all the sibs (II, III, and IV) are combined with the propositi and compared with the controls, $0.02 < P < 0.05$. When the method suggested by Smith is employed (Clarke *et al.*, 1956), which considers each sibship separately, an excess of group O in gastric ulcer propositi (observed) compared with that expected is noted.

In the past, when the Smith method has been used in analysing the data, the working hypothesis has been that a difference between the ABO blood group frequencies of the propositi and sibs might be found. A two-tail test has been used, based on the assumption that this difference might be either an increase or a decrease in O frequency. However, in view of the overwhelming evidence indicating an increase in blood group O frequency in peptic ulcer, and in the light of the work of Clarke *et al.*, an increase in group O frequency is to be expected. If this occurs, then the one-tail test perhaps provides a more valid measure of the significance of the observed differences. The raw data and the P values obtained when the one- and two-tail tests are used in the analysis of the gastric ulcer, and the previously published duodenal ulcer sibship data (Buckwalter *et al.*, 1960) by Smith's method, are recorded in Table II. Note the relatively high level of statistical significance found when the duodenal and gastric ulcer data are combined.

Only two of the gastric ulcer sibships segregated for group O and ulcer after the propositi were excluded. The basic data are included so that other investigators may, if they wish, combine these data with their own in examining the chance of an affected sib being group O with the propositi excluded:

O expected, 0.9286; O observed, 1.0000;
variance, 0.4949.

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The gastric carcinoma data show increases in the blood type A frequencies of the propiiti (I) and in all sibs (II, III, and IV) as compared with controls (V) (Table III). These differences do not have statistical significance when tested by the chi-square method. When the method of Smith is used an excess of group A in propiiti (observed) compared with that expected is noted. This difference is not statistically significant, using either the one- or the two-tail test (Table IV).

Discussion

The differences between the ABO blood type frequencies of the propiiti and the controls, characterized by an increased frequency of type O in gastric ulcer and type A in gastric carcinoma, are in accordance with our previous findings. The lower level of significance in gastric ulcer and the absence of significance in gastric carcinoma, compared with the previous report, reflect the smaller number of patients in the current study. The actual differences between the patient and control blood-type frequencies are of greater magnitude in the current study.

TABLE I.—Blood Groups of Propiiti (Gastric Ulcer Patients) and Their Siblings

Blood Type	I Propiiti		II Affected Sibs		III Unaffected Sibs		IV Unknown Sibs		V Population Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
O	137	52.9	13	61.9	160	47.3	31	50.0	22,392	44.8
A	87	33.6	4	19.0	146	43.2	26	41.9	21,144	42.3
B	27	10.4	4	19.0	23	6.8	4	6.5	4,695	9.4
AB	8	3.1	0	0.0	9	2.7	1	1.6	1,748	3.5
Total	259	100.0	21	99.9	338	100.0	62	100.0	49,979	100.0

TABLE II.—Analysis of the Chance of the Propiiti Being Group O in the Sibships Segregating for Blood Group O

	No. of Sibships	Group O Observed	Group O Expected	Variance
Gastric ulcer ..	47	28	23.4188	10.7614
Duodenal ..*	96	56	46.9797	22.0082
Combined data	143	84	70.3985	32.7696

From which we obtain:

$$\begin{array}{lcl}
 \text{Gastric ulcer: } \frac{28-23.4188}{\sqrt{10.7614}} = \frac{4.5812}{3.280} = 1.40 & \text{One-tail Test} & 0.05 < P < 0.10 \\
 \text{Duodenal ..} \frac{56-46.9797}{\sqrt{22.0082}} = \frac{9.0203}{4.691} = 1.92 & \text{Two-tail Test} & 0.10 < P \\
 \text{Combined data: } \frac{84-70.3985}{\sqrt{32.7696}} = \frac{13.6015}{5.724} = 2.38 & & 0.02 < P < 0.05 \\
 & & 0.001 < P < 0.01 \\
 & & 0.01 < P < 0.02
 \end{array}$$

* Buckwalter *et al.* (1960).

TABLE III.—Blood Groups of Propiiti (Gastric Carcinoma Patients) and Their Siblings

Blood Type	I Propiiti		II Affected Sibs		III Unaffected Sibs		IV Unknown Sibs		V Population Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
O	37	36.3	3	60.0	123	44.4	19	35.9	22,392	44.8
A	52	51.0	1	20.0	119	43.0	29	54.7	21,144	42.3
B	10	9.8	1	20.0	20	7.2	5	9.4	4,695	9.4
AB	3	2.9	0	0.0	15	5.4	0	0.0	1,748	3.5
Total	102	100.0	5	100.0	277	100.0	53	100.0	49,979	100.0

TABLE IV.—Analysis of the Chance of the Propiiti Being Blood Group A in the Sibships Segregating for Blood Group A

	No. of Sibships	Group A Observed	Group A Expected	Variance
Gastric carcinoma	16	12.0000	9.8810	3.5374

$$\begin{array}{lcl}
 \text{From which we obtain } \frac{12-9.8810}{\sqrt{3.5374}} = \frac{2.1190}{1.881} = 1.13 & \text{One-tail Test} & 0.10 < P \\
 & \text{Two-tail Test} & 0.10 < P
 \end{array}$$

Since gastric ulcer sibships were selected through propiiti with a high group O frequency—that is, 52.9%—a high O frequency would be expected in their sibs as well. This is borne out by our data; a similarly high O frequency in sibs was noted in the duodenal ulcer sibship study. Similarly, in gastric carcinoma, the propiiti high in blood type A had siblings also high in A. These findings are consistent with the population stratification hypothesis for the association between the ABO blood groups and gastric ulcer, duodenal ulcer, and gastric carcinoma.

With Smith's method—the most and perhaps only meaningful method suggested to date for analysis of sibship data—differences between the propiiti and unaffected sibs are observed which cannot be explained by population stratification and which support the cause-and-effect hypothesis. The differences between the expected and observed which are of borderline statistical significance, using either the one- or the two-tail test, are in the expected direction and are consistent with as large blood-group associations as have been found.

The finding of an increased frequency of group O in the 47 gastric ulcer sibships, similar to that observed in the 97 duodenal ulcer sibships, suggests common factors, genetic and other, for duodenal and gastric ulcer. The results of our blood-group studies showing an excess of group O in gastric ulcer provide further support for this concept. Clarke *et al.* (1955) have found no increased group O frequency in gastric ulcer patients. However, the results of their duodenal ulcer sibship and blood-group studies agree with ours (Clarke *et al.*, 1956). Differences in case selection related to diagnostic methods and criteria seem an unlikely explanation for the discrepancies between our findings and those of Clarke *et al.* in gastric ulcer. Clinical practices in Iowa and Liverpool do not greatly differ. It is unlikely that sufficient numbers of duodenal ulcer patients were inadvertently included in the gastric ulcer group in our study to cause the observed discrepancy. It is more likely that the discrepancy is due to chance. Studies as large as the Liverpool one can easily give a negative result for an association of the magnitude suggested for gastric ulcer based on data collected by 1957 (Roberts, 1957b). Sibling studies in the Liverpool gastric ulcer patients would be of interest in view of the above.

Assuming that duodenal and gastric ulcer are related diseases with common genetic and other factors, we combined our sibship data. Better justification for combining the duodenal and gastric ulcer data for analysis (Roberts, 1961, personal communication) is that an excess of blood type O is expected in each disease. By combining and analysing the data, the excess of O in the propiiti, compared with their unaffected sibs, appears to be definitely significant statistically (Table II). This provides additional support for the cause-and-effect explanation for the association of ABO blood group and peptic ulcer.

Perhaps the strongest factor influencing the incidence of peptic ulceration is sex. This variable has been removed in analysing the data by a method suggested by Roberts (1957a) (Table V). When the sibs of the sex opposite to that of the propiiti are eliminated, the number of sibships which may be used in the analysis is reduced. Note, however, that in both duodenal and gastric ulcer the observed frequency of group O still exceeds that expected, although the probabilities are lower than in the previous analysis, in which sex was not considered.

The mean age of patients with gastric carcinoma is much higher than that of those with peptic ulceration. Because of fewer numbers of surviving sibs, the accumulation of sibship data is more difficult. Excesses of group A were noted when the propoiti were compared with the unaffected sibs and with the population controls. An excess of A was also found in the propoiti of the 16 sibships segregating for group A. None of these differences were of statistical significance. All that

TABLE V.—Analysis of the Chance of the Propoiti Having Group O in the Sibships Segregating for Blood Group O After Sibs of the Sex Opposite that of the Propoiti are Removed

	No. of Sibships	Group O Observed	Group O Expected	Variance
Gastric ulcer	32	19	15.8166	7.7051
Duodenal „*	65	35	29.9413	15.2293
Combined data	97	54	45.7579	22.9344

From which we obtain:

	One-tail Test	Two-tail Test
Gastric ulcer:	$\frac{19-15.8166}{\sqrt{7.7051}} = \frac{3.1834}{2.776} = 1.15$	0.10 < P
Duodenal „	$\frac{35-29.9413}{\sqrt{15.2293}} = \frac{5.0587}{3.902} = 1.30$	0.05 < P < 0.10
Combined data:	$\frac{54-45.7579}{\sqrt{22.9344}} = \frac{8.2421}{4.789} = 1.72$	0.02 < P < 0.05

* Buckwalter *et al.* (1960).

may be said is that these data are consistent with the causal explanation for the association of blood group and carcinoma of the stomach. The most important reason for publishing these data is to make them available for the use of other investigators in evaluating their findings.

Conclusions

Evidence is presented of an increased frequency of blood group O in gastric ulcer patients, in the siblings of gastric ulcer patients, and in the patients as compared with their siblings.

These data have been combined with the previously published duodenal ulcer findings, which show similar increases in O frequency. Additional support for a causal explanation of the association of the ABO blood groups with peptic ulceration is provided.

The findings in the gastric carcinoma sibship study, based on fewer data, are less convincing, but show an excess of blood group A in patients, their siblings, and in the patients compared with their siblings.

The original manuscript was reviewed by Dr. J. A. Fraser Roberts. The reader has thereby been provided with a more critically reasoned and precisely stated report of our findings. We are fully responsible for the shortcomings of this report.

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The North of England Industrial Health Advisory Service is publishing a *Bulletin* two or three times a year and will send it to all member firms. The service is sponsored jointly by local management, the Trades Union Council, and King's College, Newcastle upon Tyne, and its headquarters are at 52 Leazes Terrace, Newcastle upon Tyne 1.

Medical Memoranda

Case of Adder-bite with Thrombosis of the Saphenous Vein

The noxious effects of adder-bite are usually insignificant compared with the fear and alarm engendered by such an occurrence. Nevertheless, venom from *Vipera berus* may place the life of a child in jeopardy, as described below.

CASE HISTORY

At 7 p.m. on June 21, 1960, a healthy 5-year-old boy living in a remote rural area of Argyll complained of a painful and swollen left ankle. It was discoloured and flecked with blood on the medial aspect. The boy's statement that his ankle had been injured "in a door" was believed. One hour later he began to vomit, and this continued intermittently for 24 hours. By 10 p.m. the discoloration had spread from the ankle to mid-thigh, and the child was delirious and in considerable pain.

Next day he was seen by a local practitioner, who sent him to the West Highland Hospital, Oban, some 30 miles (48 km.) distant. At this point he admitted having been bitten by a "big worm" while engaged with his brother in the strictly forbidden sport of trying to throw a snake on to the roof of the cottage. The boy was given 100 mg. of hydrocortisone and transferred by ambulance to the Royal Hospital for Sick Children, Glasgow, where he was admitted at 5 p.m. on June 22. Prior to his arrival antivenin had been obtained from Edinburgh.

On admission he was profoundly shocked and restless, with a very striking and persistent head-shaking movement. He was mentally confused and markedly dehydrated. The radial pulses were not palpable. The blood-pressure could not be recorded, and the heart sounds were rapid and of very poor quality.

The entire left leg was grossly swollen, the skin being tense, shining, mottled dark blue, purple, and yellow, with a sharp line of demarcation just below the inguinal ligament. Neither the femoral nor any other arterial pulse could be felt in the left leg or foot. Two small puncture wounds were visible on the medial aspect of the ankle, and the long saphenous vein was thrombosed.

Resuscitation and treatment for shock were carried out promptly in the form of intravenous infusion with injection of promethazine hydrochloride and adrenaline. Sedation was given by the use of intramuscular paraldehyde. The general condition improved rapidly and the systolic blood-pressure reached 130 mm. Hg. Intramuscular penicillin and oral tetracycline were started and continued. A small incision was made at the area of the bite, and 5 ml. of antivenin (Pasteur Institute E.R. serum) infiltrated locally. A further 5 ml. was injected intramuscularly into the opposite thigh.

Next morning (June 23) he was no longer shocked and was hydrated. Mental confusion persisted, with repetitive shaking of the head, and he appeared to be in great pain. The affected leg was enormously swollen with no palpable arterial pulsation present. Two injections of hyaluronidase were given into the thigh, but these were followed by only a minor transient diminution in the circumference of the limb.

By June 24 the discoloured area had crept above the inguinal ligament and the leg was cold. The boy was still confused, and his blood urea had risen to 83 mg./100 ml. Seventy-two hours after the adder-bite (and after much consideration) an injection of 5,000 units of chymotrypsin was given intramuscularly into the opposite thigh. This resulted in three things: (a) a brisk general reaction causing mild shock occurred 30 minutes after the injection and lasted one hour; (b) the area of inflammatory swelling and tissue discoloration spread from the left iliac fossa to the left