other members of the family. This will often bring to light several undiagnosed cases, and, as the disease in any one family tends to breed true to type, the management of the individual is assisted by further knowledge of the family.

Summary

Tuberous sclerosis is a rare disorder of tissue growth, in which many different tissues may be involved. It is hereditary and may be familial: an Anglo-Maltese family is here described in which four members were affected. The classic descriptions of the disease, to which the name epiloia was given, concentrated on the symptom triad of infantile epilepsy, mental deficiency, and adenoma sebaceum of the face, and emphasized the bad prognosis. But only about half the sufferers exhibit the disease in this fully developed form, and milder forms with good prognosis occur just as often as the severe ones. The disease is very pleomorphic, and other common manifestations are renal or retinal tumours, and cystic lungs and phalanges. The disease is probably transmitted by an incompletely dominant gene, and in any affected family the pattern of the disease remains constant. Whenever tuberous sclerosis is suspected or diagnosed in a patient the remaining members of the family should be studied.

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THE BLOOD GROUPS IN PEPTIC ULCERATION

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Evidence continues to accumulate that there is a distinct relationship between the ABO blood groups and certain diseases. The incidence of Group A has been shown to be unduly high in subjects suffering from pernicious anaemia (Buchanan and Higley, 1921), carcinoma of the stomach (Aird *et al.*, 1953), and bronchopneumonia in infancy (Struthers, 1951). Group O has been found to occur with excessive frequency in persons suffering from peptic ulcer (Aird *et al.*, 1954). It has been pointed out (Clarke *et al.*, 1955) that in the latter disease the Group O excess is confined to duodenal ulcer subjects. The present communication on the relationship of the ABO blood groups to peptic ulcer was prompted by previous investigations relating to patients in selected English hospitals. In Scotland, important differences exist both in the prevalence of peptic ulcer in general and in the geographic distribution of the ABO blood groups. Duodenal ulcers, as opposed to gastric ulcers, are between three and four times more frequent in Glasgow than in London (Doll, 1952); Group O is also present in a slightly greater proportion of the population than in England, Group A being correspondingly diminished.

This communication reports the results of a survey, carried out in Glasgow, into the ABO Rh(D) blood-group distribution in 2,059 patients suffering from peptic ulcer. In 276 of these subjects we have also investigated the maximum acid output of the stomach in relation to the above blood groups.

Collection of Data and Controls

The survey was carried out in two adjacent Glasgow Hospitals. The peptic ulcer clinic of the Western Infirmary supplied information relating to 1,588 cases, collected over the period 1946–55. Data concerning a further 471 subjects were obtained from the Southern General Hospital for the years 1952–5. Both in-patients and out-patients were included. The following items were recorded for each patient: site of ulcer, method of diagnosis, occurrence of previous acute complication, ABO group, sex, age, and place of residence. In 1,606 subjects the rhesus group was also noted.

It is obviously essential in a study of this type to ensure accuracy in diagnosis and in blood-grouping methods. Our criterion of diagnosis in 1,177 cases has been visualization of the ulcer at operation. In the remaining 882 patients the diagnosis has been accepted when a chronic peptic ulcer has been demonstrated by barium-meal examination and has confirmed a presumptive clinical diagnosis. These two groups of patients have been subsequently analysed separately, for we have been interested to discover whether any difference in blood-group frequency existed between patients diagnosed by *x*-ray examination and treated medically in the first instance, and those, presumably cases of a more severe nature, who required operation at some stage of the disease. The blood groups of the ulcer patients were determined at the Regional Blood Transfusion Centre in Glasgow for the Western Infirmary cases, and in the pathology department, Southern General Hospital, for patients from that hospital. The blood groups were specially determined for this investigation, freshly collected venous blood specimens being used. The ABO group was established by testing both cells and serum. The Rh(D) group was established, using two potent saline agglutinating sera. The control series was provided by 5,898 consecutive new registrations of blood donors at the Regional Blood Transfusion centre made over the period 1952–5. According to their location, the ulcers have been classified as duodenal, including juxtapyloric; gastric; combined gastric and duodenal; and stomal.

An explanation of the excess of Group O in duodenal ulcer patients recorded by previous authors may be that there is an association between possession of blood Group O and excessive output of acid by the stomach (Koster *et al.*, 1955). We have investigated this possibility. The augmented histamine test (Kay, 1953) was carried out on 276 patients in whom the diagnosis of peptic ulcer and the ABO Rh(D) blood groups had previously been established.

Results

The basic data are recorded in Table I. The percentage increase of Group O over controls for each subgroup of cases is indicated in Table II. Although an increase is recorded in each instance, subsequent analysis reveals that only in some of the subgroups is this increase of statistical significance. Certain comparisons have been made within the material, subdividing it in a variety of ways. The primary subgrouping has been according to the site of the ulcer. In addition, our aim has been to ascertain whether clinical severity or site of the ulcer is mainly responsible

TABLE I.—*Basic Data*

	O	A	B	AB	Total
Controls	3,177	1,906	637	178	5,898
Total peptic ulcers	1,200	630	182	47	2,059
Duodenal ,,	947	517	145	33	1,642
Gastric ,,	174	90	27	9	300
Combined duodenal and gastric ulcers	24	9	5	0	38
Stomal ulcers	55	14	5	5	79
Duodenal ulcers, operative diagnosis	505	270	71	20	866
,, ,, *X*-ray diagnosis	442	247	74	13	776
Gastric ulcers, operative diagnosis	113	55	20	6	194
,, ,, *X*-ray diagnosis	61	35	7	3	106
All cases with haemorrhage or perforation	339	163	42	13	557
Duodenal ulcers with haemorrhage or perforation	279	136	33	11	459
Gastric ulcers with haemorrhage or perforation	35	15	3	2	55
Rhesus group: all ulcers	Positive, 1,319; negative, 287				1,606
Controls	,, 4,899; ,, 999				5,898

TABLE II.—*Percentage Group Frequencies*

	Total No.	O	% Increase on Controls	A	B	AB
Controls	5,898	53·87		32·32	10·80	3·02
Total peptic ulcers	2,059	58·28	8·18	30·59	8·84	2·28
Duodenal ulcers	1,642	57·68	7·05	31·49	8·83	2·01
Gastric ulcers	300	58·00	7·67	30·00	9·00	3·00
Combined duodenal and gastric ulcers	38	63·16	17·24	23·68	13·16	0·00
Stomal ulcers	79	69·63	29·25	17·72	6·33	6·33
Duodenal ulcers, operative diagnosis	866	58·31	8·22	31·18	8·20	2·31
Duodenal ulcers, *X*-ray diagnosis	776	56·96	5·73	31·83	9·53	1·67
Gastric ulcers, operative diagnosis	194	58·25	8·13	28·35	10·30	3·09
Gastric ulcers, *X*-ray diagnosis	106	57·54	6·81	33·02	6·60	2·83
All cases with haemorrhage or perforation	557	60·85	12·96	29·27	7·54	2·33
Duodenal ulcers with haemorrhate or perforation	459	60·78	12·82	29·63	7·19	2·40
Gastric ulcers with haemorrhage or perforation	55	63·67	18·19	27·26	5·45	3·63
Rhesus-group frequency: all ulcers	1,606	Positive, 82·13; negative, 17·87				
Controls	5,898	,, 83·10; ,, 16·90				

for the increase in Group O frequency. The duodenal and gastric ulcer groups have therefore been subdivided according to the method of diagnosis and presence of complications, on the assumption that a diagnosis based primarily on operative evidence or presentation with haemorrhage or perforation denoted a more severe type of ulcer. The diagnosis was confirmed surgically in all cases of stomal ulcer.

In analysing our figures we have compared Group O against Groups A, B, and AB individually, and not against these groups combined together. Table II shows that when Group O is increased it is not necessarily at the expense of Groups A, B, and AB to an equal extent. In certain cases when Group O is increased one of the other groups is also increased. Therefore, our χ^2 tests being in terms of all four groups, there are three degrees of freedom throughout.

Peptic Ulcer: All Cases.—The proportion of patients having Group O is considerably increased; this is statistically significant ($\chi^2=15.39$, $P<0.01$). The rhesus group distribution of 1,606 patients is recorded, and shows no significant difference from the control series ($\chi^2=0.8$): in this respect Aird *et al.* (1954) report similar findings.

Duodenal Ulcer.—A significant increase is present in the frequency of Group O in the duodenal ulcer patients compared with the controls ($\chi^2=13.15$, $P<0.01$). The results have been further analysed, depending on the occurrence of complications and the method of diagnosis. All the peptic ulcer patients who sustained haemorrhage or perforation show an excess of Group O, and this is statistically signficant ($\chi^2=11.99$, $P<0.01$). Among this group the duodenal ulcer patients are responsible for the increase in frequency of Group O ($\chi^2=10.88$, $P<0.01$), to which the gastric ulcer subjects do not contribute ($\chi^2=4.06$, $P>0.05$). In the duodenal ulcer patients whose disease was so severe as to warrant operation the increase in Group O is again significant ($\chi^2=9.21$, $0.02<P<0.05$); in contrast, among those in whom diagnosis has been confirmed by barium-meal examination it is observed that the increase in Group O, while still manifest, is no longer statistically significant ($\chi^2=6.6$, $P>0.05$). However, comparing those cases with haematemesis and perforation against the rest, there is no significant difference ($\chi^2=2.76$, $P>0.05$). Also comparing the duodenal ulcers submitted to surgery and those confirmed by *x*-ray examination only, there is again no significant difference ($\chi^2=1.911$, $P>0.05$). The results suggest that the more severe cases—those that required surgical treatment—make the greater contribution to the observed increase in frequency of Group O, although the difference is not statistically significant.

Gastric Ulcer.—In our series no significant difference was noted between the ABO group frequencies of patients with gastric ulcer and the controls ($\chi^2=2.24$, $P>0.05$). In actual fact, the percentage of Group O is higher in this group than in duodenal ulcer. The non-significance may be due to the smaller number of gastric ulcers (300) compared with those of duodenal ulcers (1,642). The total number of patients who had both gastric and duodenal ulcers was too small for separate analysis.

Stomal Ulcer.—The percentage increase of Group O compared with controls was greater in stomal ulcer than in any other subgroup. Although the number of stomal ulcer patients is comparatively small, statistically the excess of Group O is highly significant ($\chi^2=13.00$, $P<0.01$). Comparing the figures for stomal ulcer against all other sites of ulceration, the difference is significant ($\chi^2=7.815$, $P<0.05$). In 68 of our 79 patients the site of previous ulceration had been duodenal (Table III), and this would suggest a possible

TABLE III.—*Site of Previous Peptic Ulcer in 79 Cases of Stomal Ulcer*

Duodenal	68	Duodenal and gastric	1
Gastric	3	Not recorded	7

explanation of our findings. However, the possibility cannot be excluded that the greatly increased incidence of Group O in patients having stomal ulcers is a particular attribute of ulcers in this situation.

Age and Sex

Since Aird *et al.* (1954) have been unable to detect any significant difference in sex proportion or age between ulcer patients of the four ABO groups, we considered that further investigation along these lines was not justified at this time. Instead our object has been to detect whether our cases constitute a representative sample of the ulcer patients treated at the hospitals in this area. No information is available concerning patients at the Southern General Hospital, from which the smaller number of our cases were drawn.

TABLE IV.—*Peptic Ulcer: Sex and Site Distribution. Comparison with Recent Series (Jamieson et al., 1949)*

Sex and Site Distribution			Male : Female Ratio		Gastric : Duodenal Ratio	
Site	Male	Female	Present Series	Jamieson *et al.* (1949)	Present Series	Jamieson *et al.* (1949)
Duodenal	1,321	321	4·12 : 1	3·9 : 1	Male	
Gastric	214	86	2·49 : 1	1·8 : 1	1 : 6·17	1 : 9·5
"Double" ulcer, G.U. and D.U.	34	4	8·50 : 1	2·7 : 1	Female	
Stomal	70	9	7·77 : 1	4·2 : 1	1 : 3·73	1 : 4·5
Total	1,639	420	3·90 : 1	3·5 : 1		

However, at the Western Infirmary, a two-year survey of ulcer patients has been carried out (Jamieson *et al.*, 1949), in which information concerning a total of 3,258 patients was analysed. In Table IV we have recorded the site, distribution, and sex of our ulcer cases, and also the male:female ratio and the gastric:duodenal ulcer ratio, together with the results obtained by the previous authors. Excluding the cases of "double" and of "stomal" ulcers, in which the numbers are so small as to vitiate useful comparison, it will be observed that no gross dissimilarities are present. In our series a slightly elevated male:female ratio in gastric ulcer subjects with an associated depression of the gastric:duodenal ratio has been caused by a relative excess of gastric ulcers, predominantly in our male patients. While a real alteration in incidence of gastric ulcer cannot be excluded, this finding is probably due to the increasing percentage of gastric ulcers submitted to surgery, these patients having been drawn exclusively from a surgical unit.

Maximum Acid Output

In 276 patients in whom the ABO group and site of ulcer were known the maximum acid output of the stomach has been estimated. The results are presented in Tables V and VI. The maximum output in the duodenal and gastric ulcer subjects displayed the typical pattern of response to

TABLE V.—*Duodenal and Gastric Ulcer: Results of Maximum Acid Output Tests*

Blood Group	Duodenal		Gastric	
	No. of Cases	Acid Output. Mean Level	No. of Cases	Acid Output. Mean Level
O	136	671 mg./45 mins.	24	404 mg./45 mins.
A	73	653 ,, ,,	15	292 ,, ,,
B	17	621 ,, ,,	6	320 ,, ,,
AB	4	726 ,, ,,	1	460 ,, ,,
Total	230		46	

TABLE VI.—*Duodenal and Gastric Ulcer: Statistical Relationship of ABO Blood Group and Maximum Acid Output*

Duodenal			Gastric		
Difference in Acid Output	P	Remark	Difference in Acid Output	P	Remark
O–A = +18	>0·05	Not significant	O–A = +112	>0·05	Not significant
A–B = +32	>0·05	,, ,,	A–B = − 28	>0·05	,, ,,
O–B = +50	>0·05	,, ,,	O–B = − 54	>0·05	,, ,,

be expected in the presence of these lesions : in duodenal ulcer it was above, and in gastric ulcer within, the accepted normal range. No significant correlation could be demonstrated between acid output and blood group in either condition.

Discussion

The outstanding fact emerging from recent investigations into the relationship of ABO blood groups to disease is that the groups have a selective value, conferring a relative immunity or susceptibility to certain disorders. Further, in adult life, alterations in blood-group distribution occur most strikingly in association with pathological lesions of the stomach and duodenum. In this communication an excess of Group O is again recorded in duodenal ulcer patients. We have also been able to demonstrate a statistically significant Group O excess over the controls in duodenal ulcer when surgical treatment was required but not when the diagnosis was made by *x*-ray examination in the first instance, although these two groups do not differ significantly from each other. This difference may not be real, and would require a larger series to confirm or refute the possibility that an increased frequency in Group O is more marked in the more severe type of case. Further work would be required before the relationship, if any, between Group O excess and severity in duodenal ulcer could be established. Similar considerations apply to stomal ulcer, which is recognized to be one of the most intractable forms of peptic ulceration. In this type the considerable Group O excess may be attributable either specifically to the site of the ulcer or to the duodenal ulcer which so often precedes it.

The selection of a control group presents a well-recognized difficulty (Allan, 1954). Hospital patients are unsuitable, because a proportion of them suffer from diseases which are known to have associations with certain blood groups. For example, at the Western Infirmary, Glasgow, in the period 1946–8, 4.3% of in-patients and 10% of out-patients were shown to be suffering from peptic ulcer (Jamieson *et al.*, 1949). We have therefore relied on data made available by the Regional Blood Transfusion Centre in Glasgow concerning consecutive donor registrations collected over a recent period.

Thomsen (1927) suggested that the distribution of the blood groups changed with increasing age. On theoretical grounds this is unlikely, as the human blood groups are widely accepted as being immutable inherited characteristics. Bryde Andersen (1955) has since failed to confirm the presence of a relationship between age and ABO group distribution, and Aird *et al.* (1954), with one possible exception, did not observe any significant difference in age between ulcer patients of the four blood groups.

The reason for the excessive frequency of Group O in peptic ulcer subjects remains obscure. Koster *et al.* (1955) have pointed out that there is an association between high acid output by the stomach, duodenal ulcer, and excess of Group O ; by contrast, achlorhydria is associated with gastric cancer and excess of Group A. If, in fact, an unduly high output of acid occurred in duodenal ulcer patients of Group O, this would suggest an explanation of the observed difference in ABO group frequencies, but we have failed to establish any such correlation. Although the blood-group substances cannot be shown to influence the secretion of hydrochloric acid, clearly they have some important role in gastric physiology, and further investigations are proceeding in order to determine its nature.

Summary

The distribution of the ABO blood groups among 2,059 peptic ulcer patients in two Glasgow hospitals has been investigated. A total of 5,898 consecutive donor registrations at the Blood Transfusion Centre supplied a control series. An increased frequency of Group O was recorded in patients suffering from duodenal ulcer, but the blood-group distribution in cases of gastric ulcer did not differ significantly from that of the controls, probably because the number of cases with gastric ulcer was too small. Among the duodenal ulcer patients, those requiring operation made the greater contribution to the Group O excess. The frequency of Group O was greatly increased in patients having stomal ulcers. Compared with controls, no difference in frequency of rhesus-negative subjects was observed.

The maximum acid output has been estimated in 276 patients with duodenal or gastric ulcer. No correlation was noted between acid output and ABO group in ulcers at either site.

The results of a peptic ulcer survey at one of the hospitals involved enable us to submit evidence suggesting that the patients concerned in this investigation constitute a fairly representative sample of those attending or admitted to hospital in this area.

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MENTAL SYMPTOMS IN PARKINSONISM FOLLOWING BENZHEXOL HYDROCHLORIDE THERAPY

BY

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It has been stated that the history of the treatment of Parkinsonism is strewn with the corpses of remedies which have fallen into disuse after an initial period of popularity (Montuschi, 1949). This is an opinion which no one will refute. During the last ten years there has been introduced a group of drugs which show definite usefulness in the alleviation of some of the distressing symptoms of the disease. The condition, which is mainly slowly progressive, although about 30% of post-encephalitic cases seem to be static, is stated to affect as many as 1 in 1,700 of the population, which means that roughly there are 27,000 sufferers in the United Kingdom (Garland, 1950), so that any treatment which promises to ameliorate the lot of such a group deserves wide consideration.

Since 1882, drugs of the family Solanaceae have held pride of place in the treatment of Parkinsonism, but it is only since 1929 that massive dosage has been used, often with undesirable results. The toxic effects—dryness of the mouth, dilatation of the pupils, and excitement passing into delirium—are well enough known to need no further emphasis here.

The piperidyl group of compounds, of which benzhexol hydrochloride is a member, has a similar action to the solanaceous alkaloids, but, although the antispasmodic effect is comparable, the toxic effects are stated to be much less, and clinical experience confirms this claim.

Benzhexol hydrochloride ("artane," "pipanol"), the drug of choice in our opinion, which was used in the cases reported below, was investigated by Cunningham *et al.* (1949), who found that when compared with atropine it was half as powerfully antispasmodic on isolated intestinal muscle; one-third as powerfully mydriatic; one-eighth as powerful as an anti-sialagogue; and one-tenth as powerful as a cardio-vagal inhibitor. It is also stated to have no acute or chronic toxic effect on blood, bone marrow, kidney, liver, or reproductive functions, blood pressure, or blood sugar. The same workers reported that in small doses the parasympathetic olytic effects are accompanied by mild depression of the central nervous system and in large doses by excitement. It is only latterly that we have come to realize that even relatively small doses of benzhexol hydrochloride may produce mental disturbance as an obvious toxic effect, and in a group of 52 patients suffering from Parkinsonism treated during the last four years no fewer than 10 have shown mental disturbances.

Case Reports

Case 1.—A man aged 65 with well-advanced Parkinsonism came under our observation in 1951. He had suffered from this condition for 16 years and had previously been treated with hyoscine hydrobromide; then for a time he was placed on benzhexol hydrochloride and, later, on ethopropazine hydrochloride. Under both of these drugs some improvement was noted, but there was no recorded reason for the change. In January, 1952, he sustained a fracture of the neck of the femur, and, probably as a result, his symptoms of Parkinsonism began to increase. In August, as he did not seem to be improving, he was placed on gradually increasing doses of benzhexol hydrochloride to 20 mg. daily, when he became mentally confused and had mild delusions. On October 1 he made an abortive attempt at suicide. After a period in an observation ward he improved mentally and he returned to this unit. He had ceased to take the drug. It was not renewed, but by December his symptoms were again marked and he was put on ethopropazine hydrochloride. He gradually showed mild confusion over the next 18 months, with delusional periods, but when he attempted to climb over a balcony ethopropazine was stopped and his mental confusion improved and delusions subsided. However, his tremors increased and so did his rigidity, to such an extent that it was thought advisable to start with small doses of benzhexol hydrochloride, and he was put on 7.5 mg. daily. Within a few days he again became mildly confused and his delusions returned, and a further attempt at suicide caused him to be removed to a mental hospital.

Case 2.—A man aged 63 first had symptoms of Parkinsonism in 1945. These increased to such an extent that he ceased work in 1947. He was admitted to the unit in 1949, and his description in 1950 was that he walked stiffly with dragging feet, stiff arms, and marked coarse tremor. He was intelligent, co-operative, and a good witness. He was given benzhexol hydrochloride, 10 mg. daily, in September, 1950, and continued with this until January, 1952, when it was noticed that he was confused. He was therefore taken off this drug and by June he was more stable mentally, but his symptoms of Parkinsonism had increased so much that it was thought necessary to try benzhexol hydrochloride again. On a daily dosage of 7.5 mg. his symptoms of Parkinsonism improved, but he became more confused and delusional in a few days. After two days without the drug he was still confused but not delusional. Two days later he was reported to be mentally bright, but his muscle control was very poor and the tremors were much more pronounced. He was placed on hyoscine hydrobromide, 1/150 gr. (0.44 mg.) three times a day. A month or so later he was transferred to another ward, and on account of the increase of his symptoms of Parkinsonism was again