

PEPTIC ULCER :

A STUDY OF ITS PREDISPOSING FACTORS.

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## CHAPTER ONE.

## INTRODUCTION.

A peptic ulcer is a benign non-specific ulcer located in those parts of the gastro-intestinal tract bathed by gastric juice. The chronic variety, with which this thesis is concerned, originates from an acute ulcer, and in the pathogenesis of the latter probably a multiplicity of factors can operate either to impair mucosal resistance or to increase the vigour of the aggressive factors to which the mucosa is subjected. Although it is commonly stated that the cause of peptic ulcer is unknown, it is nevertheless true that when all the known facts are assembled and evaluated, the conditions for the formation of a peptic ulcer can be stated rather precisely. Probably interest and research into the peptic ulcer problem have no greater obstacles to surmount than the method of approach which sets out to discover a solitary cause for the disease, or insists that the aetiology remains completely obscure. A unitary hypothesis for the cause of peptic ulcer must always be accepted with reserve. Some important factors essential for peptic ulcer formation are already known : doubtless different factors operate in different patients. Other factors

probably await discovery. For the present it is sufficient to state that no single cause responsible for all peptic ulcers is known or seems likely to be found, and that evaluation of the known provocative agents is likely to be more rewarding to the clinical investigator than concentration on only one facet of the problem of pathogenesis. In this thesis, so far as possible, such acknowledged factors have been studied and are described as "predisposing" to the disease. It is considered possible, however, that when acting in concert they may in effect prove to be causative agents.

No attempt will be made in this work to evaluate and review in detail the enormous and growing volume of literature which has amassed around the problems of aetiology and pathogenesis of the disease. In Addendum 1 are set out the existing theories of ulcer genesis. Instead, interest has been centred on those clinical factors which can be readily elucidated by interrogation and examination of the patient, and which are customarily thought to predispose the patient to his disease. It is considered that such a study is not without value, for in all diseases if the predisposing factors can be obviated or eliminated, the proximate cause, if such exists and is operative, may not be sufficiently potent to start the disease process: peptic ulcer is doubtless no exception

to this rule. In this study it has been the aim, after making a detailed analysis of certain clinical material collected by me, to investigate and assess each possible predisposing factor in turn.

The first lucid account of the symptoms and pathology of the disease was given by Baillie in 1793, although the earliest recorded clinical description of a perforated peptic ulcer dates back to 1670 (Hurst and Stewart, 1929). The gastric and duodenal varieties were differentiated and described by Abercrombie (1828) and a few years later Cruveilhier established simple peptic ulcer as a separate entity from carcinoma of the stomach. Since those early days important changes have taken place in many aspects of the disease, and particularly in its incidence. From being an uncommon and rarely recognised disorder, peptic ulcer has now become one of the major scourges of our time - world-wide in distribution, and responsible for untold pain and misery among countless thousands of sufferers. It is singularly unfortunate for peptic ulcer victims that their disease, although responsible for a high morbidity, is associated with a low mortality rate. Were the opposite to be the case, the disorder would long ago have attracted more interest from the profession and the public. In the meantime peptic ulcer research receives little encouragement and Gastroenterology remains the Cinderella of the medical

sciences, while year by year large sums are expended on enquiries into the cause of such conditions as coronary artery disease and cancer - with results sometimes not altogether commensurate with the outlay of capital and mental energy involved. However, as the incidence of the disease increases (and there is evidence to this effect) it is possible that more interest than exists at present will arise regarding its unsolved problems. A further point of some importance is that peptic ulceration most frequently takes the form of duodenal ulcer occurring in men of the upper social classes during their most productive and energetic period of life. It is manifestly undesirable, both socially and economically, that the more gifted members of the community should be the victims to a large extent of an incapacitating disease with a high morbidity which may possibly be preventable.

The foregoing observations are well supported by the available evidence regarding the mortality and morbidity from the disease. The death rate is known to be low: in the years preceding the second World War peptic ulcer accounted for only approximately 1 per cent. of all the annual deaths in England and Wales. By contrast the clinical incidence of the disease in all Western civilisations is known to be high. The heterogenous evidence from various workers ( e.g., Jennison, 1938:

Alsted, 1942; Knutsen and Selvaag, 1947) indicates that 5 to 10 per cent of most populations suffer from ulcer in a lifetime. Although estimates based on autopsy incidence must be viewed with some reserve, the latter figures gain in significance when correlated with those of Hurst and Stewart (1929), who were able to demonstrate an active ulcer or the scar of a healed one in 9.55 per cent of 4,000 consecutive autopsies. It does not necessarily follow that such a large percentage of subjects will have manifest symptoms during life, and in practice it is often found that the total incidence in any annual survey varies from about 1 to 3 per cent of the population at risk above 20 years of age. It is possible to express these figures in a different way with added significance. From the results of the population study conducted by Doll, Avery Jones and Buckatzsch (1951) it can be estimated that a total of 1,449,000 living persons in England and Wales of all ages have, or have had, a peptic ulcer. This estimate agrees closely with that of Avery Jones and Pollak (1945) whose assessment of 1,500,000 sufferers was made on the basis of hospital experience and the national death rates for 1938. These groups of observers have further concluded that cases of peptic ulcer occupy little short of 10 per cent of all general hospital beds for adults (usually on account of complications having supervened),



and that at outpatient clinics at least 10 per cent of the new patients are dyspeptics of whom about 60 per cent have radiographic evidence of peptic ulcer. Recent Hospital Morbidity Statistics (Mackay, 1951) show that peptic ulcer is the leading cause of admission to hospital among men in this country, accounting for about 1 in every 10 male admissions. Thus it is clear that the hospital service is intimately concerned in dealing with the ravages of the disease. The general practitioner already knows that the dyspeptic patient is never far from his surgery. Fry (1952), in an analysis of a year's work in his practice, found that peptic ulcer was the third most common medical condition requiring his attention.

In many other countries peptic ulcer morbidity exhibits similar trends to that in our own. Among the chronic diseases in the United States in 1937, peptic ulcer ranked tenth as a cause of death, twelfth as a cause of loss of work, fourteenth as a cause of invalidism and twentieth as to number of cases. The incidence in the U.S. Army during the second World War was 0.3 per cent.

Not only is chronic peptic ulcer a disease of considerable morbidity and high incidence, but different authors in many countries agree that that incidence is increasing. Hansen (1937) noted a steady increase in

the incidence of the disease in Copenhagen between 1901 and 1935 amounting to over 500 per cent. During this period a complete reversal of sex incidence occurred. The increase could be accounted for neither by increase in the size of the population nor by utilisation of improved methods of diagnosis. During the same period a proportionate increase in the death rate also occurred. In the United States the official mortality rate trebled between 1900 and 1945 ( U.S. Bureau of Census, 1947), and the insured of the Metropolitan Life Insurance Company of New York showed a similar trend. The evidence collated by Tidy (1944) in this country from the Registrar - General's mortality statistics reveals a 59 per cent increase between 1921 and 1937 for the whole population over 20 years of age; the increase was due to a steep rise in the male mortality from duodenal ulcer during this period. However, while most clinicians would agree that even the circumstantial evidence for a change in incidence is strong, the rapid progress of medicine has made it difficult to compare past and present figures. The introduction of barium meal examination as a reliable method of diagnosis about 1920 has made it impossible to compare with precision the incidence of uncomplicated ulcers over a long period of time.

The dramatic episode of perforation of the ulcer rarely escapes diagnosis and has a high mortality when untreated. The change in incidence of this complication can therefore be used as a rough guide to variations in the prevalence of the disease itself. There is no doubt that the number of recognised cases of perforated peptic ulcer admitted to hospitals has increased since 1910 (De Bakey, 1940), and it is highly probable, though not certain, that this increase is in proportion to the increase in the number of recognised cases of peptic ulcer. This increase in perforations is well illustrated by the figures of Illingworth and his colleagues (1944), who found that admissions to the Western Infirmary, Glasgow increased six-fold between 1910 and 1940: they further estimated that the annual incidence in the Glasgow area doubled between 1924 and 1934. In Sweden, Bager (1929) observed a similar trend. A sharp rise in the number of perforations occurring in this country during the early years of the second World War has also been recorded by several authors (Stewart and Winsor, 1942: Rendle Short, 1942: Wilson, 1942: Riley, 1942); the Scottish authors pointed out, however, that the increase could not be correlated with possible nervous strain resulting from air-bombardment. On the hypothesis that these observed changes represent true changes in incidence,

it is reasonable to deduce that environmental factors are responsible and are consequently of importance in the aetiology of peptic ulcer.

As a result of the population study carried out by Avery Jones, Doll and Buckatzsch (1951), the incidence of chronic peptic ulcer in and around London is now known with considerable precision. No similar investigation has been carried out in Scotland, and until this situation is remedied the incidence there will remain largely speculative. London estimates cannot be superimposed on Scottish experience, for significant geographic differences undoubtedly exist in many important respects - for example, in site of the ulcer, sex incidence and mortality rates. It is to be hoped that our lack of knowledge of the general incidence of the disease in Scotland will eventually be rectified, and that a planned investigation by a team of workers similar to that carried out in London will be undertaken in the not-too-distant future. In any case it is axiomatic that before attempting to elucidate a problem, its extent and scope should be defined. For the present, as other authors have pointed out (Jamieson, Smith and Scott, 1949), a fundamental piece of information is not available.

The essential facts being still obscure, it is possible to contrast Scottish and English incidences in general terms only. As is well known, the increase in the incidence of peptic ulcer since the beginning of the century has been caused by a marked rise in the occurrence of duodenal, as opposed to gastric ulcers, and men are much more frequently affected than women. In 1945 the GU: DU ratio for men in England was 1 :3.1 (Avery Jones and Pollak, 1945) but in Glasgow on 1946-47 it was 1 : 9.5 (Jamieson, Smith and Scott, 1949). The 1947 mortality figures for Scotland (Doll, 1952) show a higher proportion of duodenal deaths than in England, and indicate that this is partly due to an excess of duodenal ulcers. In addition, Tidy (1944) has drawn attention to the disproportionate rise in the male mortality from duodenal ulcer in Scotland. Assuming the morbidity from the disease to be constantly related to its mortality rate, it can be stated with confidence that the general incidence of peptic ulcer in Scotland is no less than that obtaining in England, and may possibly exceed it. This point is stressed now in view of certain comparisons to be made subsequently. There is thus substantial evidence to support the view - shared by more than one observer ( e.g. Nicol, 1941) - that

the variation in GU : DU ratio observed above is occasioned by an absolute excess in the incidence of duodenal ulcer in Scotland : a deficiency of gastric ulcers there probably plays an additional but minor rôle. It is also of some interest to note at this point that, with regard to site incidence, Scottish and American observers have recorded closely similar figures which contrast strikingly with English experience: Jennison (1938), reporting a ten-year study of the dyspeptic employees of the Metropolitan Life Insurance Company in New York, noted a GU : DU ratio of 1 : 13.5.

The subject matter of this thesis falls naturally into several compartments. In the first part a series of 200 consecutive cases seen by me in hospital practice in the area served by the Southern Ayrshire Hospital Board are analysed, and certain features discussed as they arise. These patients were first interviewed during the period from October 1950 to January 1952. There was no conscious process of selection, and they are considered to be a representative sample of the ulcer population in this area. Many more patients than the 200 mentioned were, of course, dealt with during this period by myself and other clinicians, but at some stage or other I played a part in the investigation of each of the 200 subjects.

When a patient becomes ill from any disease, his reaction to it is governed by two fundamental considerations. The first of these is his constitution, or physical endowment; the second is the prevailing state of his natural surroundings. In other words, both heredity and environment will have a major part to play in deciding whether the individual will fall victim to a particular disorder, and if so, whether the course of the disease will be short and favourable or long, dangerous and protracted. Ulcer genesis may be viewed in a similar light. If it is assumed that a single yet unknown cause is responsible for the onset of all chronic peptic ulcers, then the hereditary endowment and environmental conditions of the subject will largely determine whether or not he develops the disease; they will also influence the subsequent course of the illness. On the other hand it may be argued that, in our present state of knowledge, constitution and environment (in the widest sense of the terms) may be responsible for the onset, and partly govern the course, of chronic peptic ulcers. Until the contrary is proved it is not without merit to regard the second assumption as correct. In this way it is possible to focus attention on aspects of the disease which may be of vital importance to the individual patient, and which invite further investigation. No firm opinion

can be offered regarding the relative importance of heredity and environment in causing peptic ulcer, or in predisposing to the disease; general biological considerations would suggest that their respective rôles are of equal significance. The second part of the work is therefore concerned with the hereditary and familial aspects of the disease. In the third section a number of environmental influences are investigated and discussed.

It may be thought that a series of only 200 cases will yield inadequate information on which to base any firm conclusions; certainly it would be manifestly unwise to make sweeping generalisations on data obtained therefrom. It might be possible, for example, to argue that a total of, say, 1,000 or more cases would be a more desirable goal. But what purpose would be served by the collection of such imposing numbers? Only a few years ago a group of Glasgow observers (Jamieson, Smith and Scott, 1949) published a detailed analysis of chronic peptic ulcer statistics with particular reference to site and sex incidence after interviewing several thousand hospital out-patients in that city. There is no reason to suppose that a disease process such as peptic ulcer, which displays certain well-defined characteristics in Glasgow, will show any marked alteration in clinical behaviour 30 or



40 miles further south. Though it has its place in peptic ulcer research, the information which can be obtained from analysis of very large numbers of cases is somewhat limited. It is noteworthy that Morris and his colleagues (1952) believe that, in the study of the natural history of disease amongst populations, simple methods and small numbers may be sufficient to give worth-while results. Dr. F. Avery Jones, a prominent British gastro-enterologist, has stated his conviction that investigation into many aspects of the disease is actually hampered in his unit by the plethora of clinical material. Those who have seen the work of his department will be able to testify to the truth of this paradox. It is possible to observe in the literature a tendency to concentrate on the disease to the relative exclusion of the patient himself. Yet peptic ulcer is a very personal ailment. No two chronic ulcers and no two peptic ulcer patients behave similarly. It is my belief that future advances in our knowledge of aetiology and of the reasons for chronicity and relapse will come from long-term experimental studies on small, selected groups of ulcer patients. This is not to suggest that previous investigations have not yielded valuable information, or that the methods used in this work are especially noteworthy. On the contrary,

so far as this thesis is concerned, only well-tried procedures have been used to obtain data. For the present ulcer research along new lines will be limited by lack of facilities, not by lack of material.

## CHAPTER TWO.

## AN ANALYSIS OF 200 AYRSHIRE CASES.

In this chapter 200 consecutive cases of proven peptic ulcer who were seen personally in the Southern Ayrshire area are analysed, and the results obtained are discussed. As a preliminary measure it is of some importance to review the available information regarding the disease as it occurs in this area. It has already been pointed out that, in Scotland, precise evidence bearing on the incidence of and morbidity from peptic ulcer is lacking. Southern Ayrshire is no exception in this respect. When reliable information on the incidence and natural history of a disease in any population at risk is desired, analysis of hospital records, certificates of incapacity and postmortem reports provide data which must be viewed with great reserve. So many variable factors operate that only rough trends can be recognised. In practice, when it is desired to determine the incidence of a disorder such as peptic ulcer in a community, it is necessary to interview either all the members of it, or a number who represent a strictly representative cross-section. Generally, a large team of investigators is required in order to undertake such a formidable

procedure. The precise Scottish incidence is therefore unknown.

By a fortunate coincidence, however, an extensive survey of hospital records has recently been carried out in Ayrshire. The survey (Hospital and Community, 1949) can, by its nature, provide only limited information about the disease as it occurs in this area. Nevertheless, the evidence it contains in respect of peptic ulcer is of considerable interest. Among the people of Ayrshire in 1948, peptic ulcer was, with the exception of appendicitis, at all ages the most common of the digestive diseases requiring inpatient hospital treatment. The number of male cases greatly outnumbered the female cases, being 415 against 76 (male: female ratio = 5.5 : 1). The number of patients per 1,000 of population treated in hospital for peptic ulcer was about double in the central district that in any other district of Ayrshire (for district boundaries see Addendum 2 - Map). It would be incorrect, however, to assume an unduly high local incidence of the disease, for at Ballochmyle hospital, which serves the central district to a large extent, there is a physician who takes a particular interest in the management of peptic ulcer cases and who conducts there a special "Gastric" Clinic. Such a clinician will

naturally attract to himself an unduly large proportion of the cases in which he specialises. In addition it should be noted that many of the male population in the central district are engaged in the occupations of mining and quarrying; as is pointed out subsequently, there is evidence to suggest that mining is an occupation in which there is an excessive incidence of peptic ulcer.

The 200 subjects of the investigation were all interviewed personally, and a standard proforma completed for each one. A proforma copy which indicates the scope of the enquiry is appended (Addendum 3). The cases were interviewed at the three major hospitals of the Southern Ayrshire Hospital Board, i.e. Ballochmyle, Heathfield and Ayr County Hospitals. The first is situated near Mauchline, and the two latter are within the boundaries of Ayr Burgh. The numbers of patients seen at each hospital were as follows :- Ballochmyle, 150 : Heathfield, 19 : Ayr County, 31. The preponderance of cases seen at Ballochmyle Hospital is due to the presence there of a "Gastric" Clinic which provides ready access to clinical material. No firm distinction was made between inpatients and outpatients, since in many instances their states became interchangeable during the course of treatment. In point of fact, however, at the time of interview 165

Table 1.

Distribution by geographical area of 200 peptic ulcer subjects residing in Ayrshire.

Area in which residing	No. of subjects
Ayr Burgh	40
Kilmarnock Burgh	4
Northern Area	25
Central Area	80
Southern Area	46
Ex - County	5
	200

were outpatients and 35 were inpatients.

### Residence of Subjects.

With 5 exceptions, all the subjects resided in Ayrshire. Their domiciliary distribution by geographical area is shown in Table 1. It will be noted that the majority of the patients came from the southern half of the county. Four of the 5 subjects who resided outside the county had their homes just outwith its borders. In such localities it is frequently equally convenient to the patient to have his hospital investigations carried out at an Ayrshire hospital, or to travel to either Glasgow in the north or to Dumfries in the south. The fifth patient, a Scotsman by birth, was in holiday in Ayrshire from his home in England when he came under observation due to a haemorrhage from his duodenal ulcer. (Table 1 near here).

### Social Class.

Social class as such is known not to have any appreciable influence on the incidence of peptic ulcer as a whole ( M.R.C. Spec. Rep. Series No. 276, 1951). The absolute numbers of the population at risk in each class, however, substantially affects the percentage of patients in each class coming under observation who suffer from the disease. This is exemplified in Table 2,

Table 2.

Distribution of 200 ulcer cases by Social Class: author's series contrasted with those obtained in recent hospital survey (1949), and results expressed as percentage.

No. of Class	Percentage of subjects in each Social Class					
	1	2	3	4	5	6
Present Series	2.5	7	33.5	35	7	15
Hospital Survey (1949)	11.1		49.9	26.9	12.1	-



in which the percentage of the patients in each social class is set out. A comparison is made between the results obtained in the present series, and those described in the recent survey of hospital - treated sickness in the Ayrshire population (Hospital and Community, 2 , 1949). Such a comparison is permissible because, in such a disease as peptic ulcer, hospital inpatient and outpatient data with regard to social class are considered to be interchangeable. Social class 6 is included in the present series, but not in the community survey : it consists of housewives not otherwise employed, and retired persons. Both series are in agreement in indicating that social classes 3 and 4 will provide 70 per cent of all ulcer patients met with in hospital practice. (Table 2 near here) .

#### Confirmation of Diagnosis.

Strict criteria of diagnosis were adopted, and the results of their application are shown in Table 3. It is possible that, in effect, some cases interviewed but not included in the series did in fact have peptic ulcers, but the aim was to include only fully proven cases. Where the diagnosis was established in consequence of perforation of the ulcer alone without any ancillary methods, treatment had been by open

Table 3.

Mode of confirmation of diagnosis in 200 cases of peptic ulcer.

Method of Diagnosis	No. of patients.
Barium Meal alone	154
Perforation, with operative closure	16
Barium Meal and Perforation	26
Laparotomy alone	2
Laparotomy and Barium Meal	2

operation. The occurrence of alimentary haemorrhage, though strongly suggestive of the presence of an ulcer, was not considered to be absolutely diagnostic. Various observers attach a different degree of significance to the event of massive alimentary haemorrhage. Avery Jones (1951) considers that in at least 90 per cent of cases haematemesis or melaena is due to a peptic ulcer; on the other hand Ivy et al. (1950) believe that peptic ulcer is the cause of only 72 per cent of upper alimentary haemorrhages. In view of this discrepancy, no reliance for diagnostic purposes has been placed in this series on the complication of haemorrhage. Laparotomy alone confirmed the diagnosis in 2 cases: it had been carried out mainly for diagnostic purposes. (Table 5 near here).

### Sex Incidence.

Since the beginning of the present century a progressive change in the incidence of the disease in the two sexes has been observed. In the early years of the century gastric ulcers among women predominated. Recent clinical evidence and mortality statistics indicate an increase in peptic ulcer incidence throughout the world, and this increase has

unequivocally involved primarily an increase in the incidence of duodenal and prepyloric ulcers in males. After an extensive survey of the world literature Ivy et al. (1950) concluded that the male : female ratio had changed from about 1 : 3 to 3 : 1 in the last 50 years. In Scotland, Jamieson et al (1949) have observed a male : female ratio for all ulcer subjects above the age of 10 years of 3.5 : 1. Their figures correlate precisely with those in the series of Knutsen and Selvaag (1947) in which the rates at ages 20 to 49 was also 3.5 : 1. In the recent London survey ( Avery Jones et al., 1951) it was 3.9 : 1. Since the incidence of ulcers varies with age, the ratio between the sexes will depend on the age constitution of the population. Unless very large numbers are dealt with, a factor of unreliability will exist due to the small numbers of female cases which will come to light. In the present series there were 171 male and 29 female cases, giving a male : female ratio of 5.9 : 1. The deficiency of female cases may be real or artificial. The latter event is considered to be more probable. Although the 200 cases were consecutive and might reasonably be expected to represent a cross-section of the peptic ulcer victims in this area, nevertheless an unconscious bias may well exist in the mind of the general practitioner who first

refers the case. In dealing with dyspeptic males the possibility of duodenal ulcer is constantly in mind, whereas in similarly afflicted females peptic ulcer, which is known to be less common among them, is diagnosed initially with all the greater caution and, conceivably, less frequently.

#### Incidence of Gastric and Duodenal Ulcers.

Thus far gastric and duodenal ulcers have been considered together as forming a single entity - peptic ulcer. They do not always show the same characteristics, however, and different factors may be concerned in their aetiology. Not only is their clinical behaviour different, but striking changes have taken place in this century in their relative incidence. Ivy et al. (1950) have observed a world trend which has altered the gastric-duodenal ratio from about 4 :1 a matter of 50 years ago to the present ratio, which in most populations they believe to be about 1 : 3. Some diversity exists between the ratios as found by various authors which can be accounted for by variations in the social structure and age groupings of the patients with whom they were dealing. Geographical differences are also known to play an important rôle. In London ,

Tidy (1944) noted an overall gastric- duodenal ratio of 2.5 : 1, while only a few years later Avery Jones and Pollak (1945) were able to record a similar ratio in males over 10 years of 1 :3.1. In Scotland, duodenal ulcers are more common and gastric ulcers less common than in England (Doll, 1952). This difference in ulcer site in the two countries is strikingly exemplified by the series of Jamieson et al (1949) in which is noted a ratio of 1:9.5 in males and 1 : 4.5 in females, again at all ages above 10 years. These ratios are of particular interest when compared with that reported by Jennison (1938). Among clerical workers in New York who had ulcers she found a ratio of 1 : 13.5. It is clear that peptic ulcer in Scotland, in respect of its site incidence occupies an intermediate position between English and North American experience.

In this series the overall gastric: duodenal ulcer ratio of the 200 cases was 1 : 14.4. Among the male subjects it was 1 : 16.1, and among the females it was 1.: 8.7. These results show similar trends to those recently reported in Glasgow. The high overall ratio in the present series is striking, however, and cannot be explained solely on the basis of limited numbers. Although the number of female cases included was small (29) the gastric: duodenal

ratio for males alone still remains unduly high. The possibility that the incidence of duodenal ulcers among Ayrshire men exceeds that in Glasgow men cannot be excluded. In both series juxta-pyloric ulcers were classified as duodenal since, as they behave in the same fashion clinically, it is now customary to do so .

#### Present Age in Relation to Age at Onset.

The age of the patient when he comes under observation bears little relation to the age at which the disease first appeared. Often a long history of dyspepsia extending over many years is obtained. In Table 4 the 200 subjects are grouped by age, and the age at interview is shown in relation to the age at onset. It will be noted that in nearly 75 per cent of cases the patients were aged 25 to 54 years when interrogated. By contrast, well over half of them were between 15 and 34 years of age at the time of onset of the disease. The observation that peptic ulcer originates in the first half of life in the majority of subjects is in accordance with the generally accepted belief that the risk of developing an ulcer falls off rather sharply after the age of 45 years (Sällström, 1945). This belief is correct for those

TABIE 4.

Age groups of 200 peptic ulcer subjects at time of onset of disease,  
and at present time.

Age Group (years)	No. of patients per age group at onset of disease.	No. of patients per age group at time of interview.
0-14	4	0
15-24	55	15
25-34	65	44
35-44	32	49
45-54	27	52
55-64	14	26
65+	3	14
All Ages	200	200



patients who actually come under treatment, but it cannot be further concluded that, for the population at large, the risk of developing a peptic ulcer is greatest in the first 3 or 4 decades of life. The numbers exposed to the risk in the higher age groups are smaller, and are also depleted by the loss of some ulcer subjects by death. Indeed, Avery Jones et al. (1951) have shown that the idea that peptic ulcers develop more frequently in young men is erroneous, and the the expectation of developing an ulcer is almost constant, being at its maximum between the ages of 35 and 64 years. (Table 4 near here).

It is of less practical value to know the average age at the onset of symptoms, but this has been calculated by a few observers. In the United States, Eustermann and Balfour (1936) concluded from an analysis of their own material that it was 33 years in the case of duodenal ulcers and 41 years in respect of gastric ulcers. These figures agree rather precisely with those noted in the present series, which were 33.3 and 41.8 years respectively.

The change in incidence of peptic ulcer with age is shown in Table 4, column 2. It is in accord with the usual teaching that peptic ulcer is infrequently encountered in patients below the age of

20 years, becomes increasingly common up to the ages of from 45 to 54 years, and then decreases in frequency.

The Duration of Ulcer History in Relation to the Onset of Complications.

The three major complications of peptic ulcer are perforation, haemorrhage and pyloric stenosis- in that order of mortality. Emery and Monroe (1935) followed 1435 ulcer patients for an average period of 3.9 years and found that :-

Perforation occurred in 7.7 per cent with a mortality rate of 1.9 per cent.

Haemorrhage occurred in 26.7 per cent with a mortality rate of 1.3 per cent.

Pyloric onstruction occurred in 11.7 per cent with a mortality rate of 0.2 per cent.

As might be expected, the longer the ulcer is present, the greater is the incidence of possible complications. It will be noted from Table 5 that major complications supervened with increasing frequency as the duration of the disease increased until, when the onset had been between 21 and 25 years previously, one or more of the possible complications had occurred in over 85 per cent of subjects. After the duration of history

Table 5.

Duration of Ulcer History in Relation to Incidence of Complications in 200 peptic ulcer subjects.

Duration of History (years)	No. of Subjects	No. of Subjects developing a major complication.
0 - 1	40	18 (45%)
2 - 5	49	12 (24.5%)
6 - 10	46	22 (48%)
11 - 15	28	13 (46.4%)
16 - 20	13	9 (69.2%)
21 - 25	7	6 (85.7%)
26	17	12 (70.6%)
	200	92

had exceeded 26 years, it was possible to observe a slight decrease in the incidence of complications: it is possible to attribute this decrease to a diminution in the activity of ulcers with advancing years. The high incidence of complications noted in the subjects who had a short history of one year or less is due to the fact that it was these same complications which brought the patients under medical observation for the first time. (Table 5 near here) .

#### Perforation.

Of all the possible complications of chronic peptic ulcer, perforation of the ulcer is the most dramatic and, even at the present time, it is still the most lethal. Various authors ( Ivy et al, 1950) have computed the number of ulcer patients who perforate at between 3 and 13 per cent: a further 1 per cent re-perforate. Illingworth (1952) calculates that in this country between 0.5 and 1 per cent of male ulcer patients will perforate in any one year. In this series no less than 42 of the 200 subjects had sustained a perforation; this unduly high proportion was occasioned by the fact that it was the occurrence of the perforation which had brought many of these patients under continued medical care. All had been treated operatively. In

Table 6.

Summary of findings in perforated peptic ulcer occurring among a series of 200 ulcer cases.

No. of Subjects Affected		42
Site of Ulcer :	Duodenal	41
	Gastric	1
Sex of Subjects:	Male	38
	Female	4
Mean Age in Years (at time of first perforation)		36.3
No. of Subjects sustaining 1 perforation		36
" " " " 2 or more perforations		6
No. of Subjects Asymptomatic until Perforation occurred.		7

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all but one case the perforated ulcer was sited in the duodenum. Four females and 38 males were affected, so that the males developed this complication 9.5 times more frequently than the females. This is in accord with the observation that perforation occurs at least 9 times more frequently in the male (Ivy et al, 1950). However, a male: female ratio of 9.5 : 1 is almost certainly too low if applied to all perforations occurring in this area. After making a survey of its frequency and incidence in the West of Scotland, Illingworth et al. (1944) showed that the ratio was in fact 19 : 1 and had remained substantially unaltered for the past 20 years.

Of the 42 subjects to whom reference has been made, 6 had sustained two or more perforations. It is known that most perforations occur between the ages of 20 and 50 years; in this series the mean age at the time of the first perforation was 36.3 years. It is also well established (de Bakey, 1940) that in about 15 per cent of cases perforation is the first indication of the presence of an ulcer; in the present series the perforation had been preceded by no dyspepsia, or only insignificant dyspepsia, in 7 ( or 16.6 per cent) of subjects. The foregoing observations are summarised in Table 6.

(Table 6 near here).

Table 7.

Summary of findings in respect of the complication of alimentary haemorrhage in a series of 200 peptic ulcer cases.

No. of Subjects Affected		51
Site of Ulcer :	Duodenal	46
	Gastric	2
	Stomal	3
Average Length of Ulcer History (years)		12.75
No. of Subjects Eupeptic before Haemorrhage occurred		4
No. of Subjects sustaining 1 haemorrhage		34
" " " " 2 haemorrhages		9
" " " " 3 to 5 "		6
" " " " 6 or more "		2

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### Haemorrhage.

Haemorrhage from the ulcer was the most common complication: it had occurred in 51 of the 200 subjects interviewed i.e., in 25.5 per cent. The proportion is of interest in view of the observations of Ivy et al. (1950), who calculate that 25 per cent of chronic ulcers bleed at some time in their course, and that a similar percentage of peptic ulcer patients who enter hospital are admitted on account of haemorrhage; also, of the ulcer patients who die from their disease, 1.6 per cent do so as a result of this complication. In this series the site of ulcer was predominantly duodenal and, as might be expected, a long history of dyspepsia (which averaged 12.75 years) was usually obtained. As in the case of perforation, the complication of haemorrhage may be the first indication that an ulcer is present; of the 51 subjects who bled, 4 ( or 8 per cent) had previously been eupeptic. These findings are summarised in Table 7.

(Table 7 near here).

### Operative Treatment.

At some point during the course of their disease 34 of the 200 ulcer patients had been subjected to elective surgical treatment. Partial gastrectomy had been performed on 17 subjects, the ulcer being



duodenal in site in 15 and gastric in location in 2. When seen within six months of their operation, all but two reported that they were in good health and entirely free from dyspepsia. The two subjects who were not yet in full health had noted a mild form of the post-gastrectomy "small stomach" syndrome; the symptoms were neither severe nor incapacitating, and the patients declared themselves satisfied by the results of their operation. Gastroenterostomy had been carried out on a further 16 patients; the ulcer had been duodenal in all but one, and in the latter case it was known to have been prepyloric. In two of these the long-term results had been good, and the patients had remained free of their dyspepsia. However, disabling sequelae had followed in the remaining 14 subjects. No less than 12 had developed a stomal ulcer, as manifested by haemorrhage in 7, perforation in 2, and formation of a gastrocolic fistula in one. The gastroenterostomy had had to be undone in one case, and a subsequent partial gastrectomy had been necessary in 2 of the subjects. One patient had also been subjected to the combined operation of pyloroplasty and vagotomy, but with poor results.

Not all the subjects operated upon had had their surgical treatment carried out in this area.

Some had been dealt with at other centres. The operation of gastroenterostomy had usually been carried out many years previously, at a time when it was in vogue for the treatment of chronic duodenal ulcer. Recent operations had consisted almost entirely of partial gastrectomies, and the majority of patients had received their surgical treatment at Ballochmyle Hospital. At this hospital it is the custom of the chief surgeon to perform the Hofmeister type of operation, which entails the formation of a retrocolic, isoperistaltic anastomosis with a valve.

Even in this small series the contrast between the results of subtotal gastrectomy and gastroenterostomy is striking. While in the former case all but two of the patients were completely free from all symptoms, in the latter all but two had severe and persistent dyspepsia. Although it is true that the postgastroenterostomy subjects represented a special group who attended hospital solely on account of their continued dyspepsia, and that some patients undoubtedly remain well after this operation, it is also noteworthy that no cases of postresection stomal ulceration were encountered. Tanner (1952) has found that anastomotic ulceration follows in as many as 30 per cent of patients who have had a gastroenterostomy. Many authorities would

consider this estimate somewhat conservative. On account of the high incidence of subsequent stomal ulceration, the operation has been largely abandoned. However, appreciable numbers of patients with stomal ulcers are still encountered in medical practice, and it is of importance to note the serious nature of the prognosis in such cases. Having reviewed the world literature, Ivy et al. (1950) point out that manifest haemorrhage occurs in 35 per cent of such patients, with stenosis of the stoma in 10 per cent, perforation in 10 per cent, and formation of a gastro-jejuno-colic fistula in a further 10 per cent. Not only is diagnosis often difficult, but operative treatment, which is eventually necessary in about 60 per cent of cases, carries an overall mortality rate of 15 per cent.

## CHAPTER THREE.

## THE INFLUENCE OF HEREDITY.

The existence of an inherited constitutional factor which gives rise to variations in the response of different species and individuals to the same stimulus is an accepted biological fact. To state that such a factor plays its part in the aetiology of peptic ulcer is therefore a biological truism. Such a factor will determine to a large extent what proportion of individuals in a population will develop the disease, and will also influence the potency of the agent or agents responsible for causing it. Although how the factor exerts its influence is unknown, perhaps the best evidence of its existence is the remarkable tendency for peptic ulcer to recur in the same patient. It is also noteworthy that no theory of ulcer genesis yet evolved is able to explain the national and racial incidence of the disease. Held and Goldbloom (1946), in their book on the subject of peptic ulcer, state that "notwithstanding other features which may be partially responsible, we are convinced that peptic ulcer does not develop without some underlying constitutional and psychosomatic element", and they further observe that such a constitutional

element may be manifest as a familial tendency. An additional point of practical importance is that it is unlikely that an inherited constitutional factor will change within two or three generations in a mixed population. If, then, the disease shows striking changes in incidence within a period of a century, it is reasonable to assume that such changes are due, in large measure, to environmental influences which are possibly both causative and preventable.

Until comparatively recent years the relative importance of the hereditary aspect of peptic ulceration has been obscure. The prevalence of the condition made the chance association of several cases in one family reasonably probable. Also, until radiology became available as a method of diagnosis, it was difficult to be certain that an ulcer was present. Several authors have recently been able to overcome these difficulties.

Many so-called "ulcer-families" have been reported. The outstanding one is that of Helweg - Larsen (1946); among 105 members spread over 5 generations, an ulcer was positively diagnosed in 13 patients and there was presumptive evidence of ulcer in a further 14 subjects. Ivy and Flood (1950) have presented a pedigree in which, of 8 siblings, 3

had proven ulcers and 2 had probable ulcers; assuming a general incidence of 5 per cent for peptic ulcer, it can be shown that the likelihood of such an ulcer incidence in an 8- children family occurring by chance is several million to one against. Such "ulcer-families" are, of course, encountered very rarely. Only one such family was met with in this series. There were 21 members in it, spread over 3 generations. An ulcer had been positively diagnosed in 6 of them, and a further 11 suffered from severe dyspepsia. The occurrence of ulcer in 5 pairs of identical twins is a finding of considerable interest reported by Freeman(1947). Riecker (1946) has noted its development at the same time in identical twins in different geographical locations; he has also reported the case of a pair of dizygotic twins whose ulcers perforated within an hour of each other. Many authors (Spiegel, 1918: Strauss, 1921: Bauer and Aschner, 1922: Huddy, 1925: Willcox, 1940: Nicol, 1941 : Sällström, 1945: Greco, 1946) have investigated the role of heredity, usually by comparing the incidence of ulcer in the near relatives of ulcer patients with that in controls. For example, Bauer and Aschner (1922) obtained a history of peptic ulcer in the parents or siblings of 255 patients with a gastric or duodenal ulcer 5

times as frequently as in 400 non-dyspeptic controls. All these authors have agreed in finding a higher incidence in ulcer families. Spiegel (1918) has pointed out, however, that the patient with an ulcer is more likely to be interested in searching out ulcer cases in his family than the patient who has an unrelated disease. Levin and Kuchur (1936) were able to overcome this objection. They compared near relatives of ulcer patients with 500 members of the general population, and reached the conclusion that ulcers were three times more frequent in the relatives of the ulcer series. It has recently been possible to apply this method in Britain. Doll, Avery Jones and Buckatsch (1950) obtained information about the general incidence of ulcer in the population. Using this information for comparison, and working in the same area, Doll and Buch (1950) have been able to compare the observed and expected incidence in ulcer families. An excess of ulcers was demonstrated in the siblings of the ulcer subjects. Further, familial tendencies were thought to be more prominent in duodenal ulcer patients. This tends to confirm the view long held (Ivy et al., 1950) that a positive family history is more commonly found among duodenal than among gastric ulcer patients.

## Methods.

The aim of the investigation reported in this chapter was to determine whether, in this area of Scotland, heredity plays an important part in the aetiology of peptic ulcer. A familial tendency to ulcer has been recorded among groups of patients in many countries, but as yet no information has been collected on the subject in Scotland. Preliminary details of the 200 subjects who form the series have been given in the previous chapter. In each case a full family history extending, when possible, over five generations was recorded, and the number of persons alive in each generation was also noted for both sexes. Although several interesting family histories were obtained, it was found when the investigation was complete that some of the information was superfluous. Only that relating to the siblings of the *propositi* was sufficiently detailed to warrant statistical analysis. There were several reasons for such a result. Firstly, due to the limitations of human memory, the *propositi* in several instances were unable to give adequate details about their more aged and distant relations in the parental generations. Secondly, too few members of the parental generations were still alive for any useful comparison between the observed and expected incidences of ulcers among them to be made. Thirdly,



many of the members of the filial generations had not yet reached an age when ulcers were liable to develop.

The problem of the provision of controls was the most difficult to surmount. Since the incidence of peptic ulcer in the general population of Scotland is still unknown, indirect methods had to be used. Two separate approaches were utilised. It was decided to apply the incidence of ulcer as estimated in Greater London by Doll et al. (1950) to the material obtained, on the assumption that the Scottish incidence was no less than, and possibly exceeded, that observed in London. The reasons why this assumption is regarded as justified are set out in Chapter One. As an additional check, 100 control cases were interviewed, from whom a full family history in respect of possible peptic ulceration was obtained. The control cases consisted of hospital inpatients who had no alimentary disease, and who had never suffered from major dyspepsia. As full details of the control cases are given in Addendum 4, a description of them is omitted here. It is only necessary to emphasise that, for purposes of comparison, they can be regarded as a representative sample of the hospital population. Obviously, the family history of any subject will not of itself be affected by his or her age, sex, present disease, or whether at any given time he or she is in or out of

hospital. There is a remote possibility that social class might affect the type of control subjects dealt with if patients confined almost entirely to one or two classes had been interviewed. In fact, however, as is shown in Addendum 4 (b), they were drawn from all social classes and were, moreover, part of the hospital population to which many members of the larger series also belonged. By means of this double check, therefore, an attempt has been made to overcome the lack of knowledge of the precise incidence of ulcer in the local population.

The criteria adopted for proof of an ulcer in any affected relative were substantially the same both in the controls and in the major series. Where a history of perforation, major gastric surgery, massive alimentary haemorrhage, or a positive barium meal finding was obtained on one or more counts, the presence of ulcer was regarded as proven. Where there was a definite history of major dyspepsia of ulcer type, but further evidence was lacking, a presumptive ulcer was considered to be present. It would have been desirable to either interrogate or send a questionnaire to those relatives thought to have an ulcer, but this was soon found to be impracticable. In too many instances the propositi were unable to give any precise information about the present addresses of

their near relatives; in not a few instances, some of the latter had emigrated. Indeed, it is possible that some ulcers have been omitted due to ignorance on the part of the subjects interviewed. Since the control series was composed of living persons, the group for comparison was confined to living relatives.

Sex and age differences are the most important variables affecting the incidence of ulcer. They have been allowed for as far as possible. The sexes have been dealt with separately. Since the 300 subjects interviewed were often vague about the precise ages of their living relatives, it has not been possible to express the incidence (observed and expected) by age groups. Instead, only living blood relations of 14 years and over in each sex are included. Similarly, the expected incidence (based on the London figures) has been calculated from the incidence which exists in the population there at all ages over 14 years for each sex. Other differences are not thought to be important. Social class differences were inconsiderable, and occupational differences were slight. Geographical and temporal differences played no part: both the ulcer series and the controls were interviewed during the same period of time. In the results which follow, siblings of the propositi who had not yet reached the

age of 14 years are excluded, since it is known that in the first decade or so of life the expectation of developing a peptic ulcer is very small.

### Results.

The incidence of ulcers in the living brothers and sisters of the propositi is shown in Table 8. The 200 propositi had 410 living brothers, of whom 55 were considered to have a peptic ulcer. Similarly, the 421 living sisters had 15 ulcer subjects among their number. If the incidence of peptic ulcer in men and women at all ages over 14 years is taken as 6.5 per cent and 1.7 per cent (M.R.C. Spec. Report Series No. 276, 1951), it can be calculated that the incidence of ulcer which might be expected in the brothers and sisters is only 26.65 and 7.2 respectively. Again, using the ulcer incidence in the male and female siblings of the 100 control subjects, it can be shown that the expected incidence from this source is 16.4 and 3.86 in the two sexes. The expected ulcers have been calculated by multiplying the number of sibs in each sex group by the incidence rates of ulcers in the two separate types of control population. In view of the objection of Spiegel (1918), to which reference has been made, that the expected ulcer incidence as calculated from a

Table 8.

Incidence of ulcers in sibs of 200 propositi, with comparison between observed and expected incidences: siblings only of 14 years and over included.

	BROTHERS	SISTERS
No. of Subjects Living	410	421
No. of Ulcers :-		
(a) Proved	30	4
(b) Presumptive	25	11
Total	55	15
No. of Ulcers expected from control series (i)	16.4	3.86
No. of Ulcers expected from known London incidence (ii)	26.65	7.2
Ratio of Observed to Expected (ii)	2 : 1	2.1 : 1.0

control series is likely to be artificially low, the expected incidence as determined from the data of the London observers is considered to be the more accurate. On this basis the minimum ratio of observed to expected ulcers in the living brothers of the propositi is 2 : 1 ; in respect of the sisters it is 2.1 : 1.0. (Table 8 near here) .

In the parental generation the data was inadequate for useful analysis; many members were no longer alive, and in a few the medical history was obscure. Nevertheless, in the living or deceased males of this generation a history of ulcer was obtained in 33 cases (18 proven, 15 presumptive), and in the opposite sex 5 cases (2 proven, 3 presumptive) were recorded. More interesting information became available when the data pertaining to the living children of the propositi was considered. Of these there were 218 sons and 214 daughters. Thirteen ( 6 per cent) of the sons were known to suffer from peptic ulcer, the diagnosis being regarded as proven in 8 and presumptive in 5. Three of the 214 daughters (1.4 per cent) were ulcer subjects, with a proven diagnosis in 1 and a presumptive diagnosis in 2.

## Discussion .

From the results presented it is clear that a significant excess of ulcers occurred among the brothers and sisters of the ulcer patients. Moreover, the ratios of observed to expected ulcers are so close ( brothers 2:1; sisters 2.1 : 1) that it is reasonable to conclude that similar factors operated in both sexes. It would have been of interest to confirm this conclusion by considering the male and female propositi separately; the latter were too few in number, however, for this method to be of value. No conclusions can be reached regarding the incidence of ulcer in the parental generation, but an ulcer incidence of 6 per cent in the living sons of the propositi is noteworthy. Such an incidence does not exceed that which might be expected in a male population, but it must be remembered that many of the children had not yet attained an age at which peptic ulcer is likely to develop. Fifty-nine of the 200 propositi had not yet reached the age of 35 years (table 4), and their sons were of tender years. The observed incidence among the sons is therefore believed to be suggestive of a familial tendency, though not conclusive.

There are several possible explanations of these results:-

1. A family history of ulcer may have influenced the selection of the cases for study.
2. Ulcers may be found more readily when one is already diagnosed in a family.
3. Similar environmental influences may be responsible.
4. Peptic ulcer may have a hereditary basis.

No conscious selection of patients was made which could have resulted in a differential selection of those with a positive family history. The cases were consecutive, and family history played no part in deciding which patients should attend hospital. Those relatives who had had peptic ulcers were diagnosed in the ordinary course of medical practice. It is true that, for the purpose of this enquiry, the diagnosis in respect of the affected relatives was based on second-hand information. However, it was found that such relatives were often widely scattered and in some instances their present whereabouts were actually unknown. Under these circumstances it was decided that, for one investigator working alone, the issuing of questionnaires or an attempt to interview relatives who might or might not be ulcer subjects was



a task which was impracticable and also unlikely to yield results commensurate with the effort involved. It is of interest to note that any population survey, such as that carried out by Avery Jones et al. (1951), will bring to light a small number of ulcers which medical practice has failed to reveal. The possibility therefore exists that some relatives of the propositi did in fact have ulcers, but are not included in the series, having evaded diagnosis. It is also possible that when one member of a family has been proved to have an ulcer other members with indigestion become more likely to be investigated, with the result that more ulcers would be diagnosed in ulcer families than in the general population. However, this possibility cannot account for the results, as the number of ulcers observed among the siblings was significantly greater than the number expected. Nor can the results be accounted for by assuming that the patients came to hospital more readily if they had relatives who had previously had ulcers diagnosed. No less than 93 of the 200 subjects had no choice in the matter. They were brought under hospital care initially due to the two major complications of peptic ulcer, i.e. perforation and haemorrhage. The possibility that similar environments may have been responsible for the results cannot be excluded. However, it is unlikely, as an

excess of ulcers was noted in one generation and a probable excess in the subsequent generation.

Environmental influences which operate from childhood are frequently dissimilar in two consecutive generations, or even among the members of one generation. In this connection the article by Riccker (1946), to which allusion has been made, assumes added significance; he noted the development of peptic ulcer in identical twins in different geographical locations.

The most reasonable explanation of the results is that hereditary factors are of importance in the production of peptic ulcers. No attempt is made to determine the mode of inheritance, as the data are inadequate. This aspect of the subject is discussed at length in a subsequent section.

In conclusion, it should be noted that peptic ulcer has been considered throughout as a single entity. Information was not available as to the site of the ulcer in those relatives who were victims of the disease. However, hereditary factors are not necessarily of equal importance in all types of ulcer. A number of authors ( Levin and Kuchur, 1936 : Nicol, 1941; Doll and Buch, 1950) have produced evidence which suggests that the family history is more strongly positive when the symptoms begin early in life, and when the

ulcer is duodenal rather than gastric in site; a tendency has also been observed for brothers and sisters to have ulcers in the same site.

## CHAPTER FOUR.

## THE INFLUENCE OF ENVIRONMENT.

Using the term in its widest sense, the environment of the ulcer patient may be said to include the basic extraneous cause of peptic ulcer (if such single cause exists), together with all the possible predisposing factors to the disease to which the subject is exposed. The present state of our knowledge suggests that the latter are numerous, although the potency of each one remains a matter for speculation. Accepted medical teaching incriminates such factors, for example, as fatigue, lack of sleep, shift work, and the hurried and irregular consumption of poorly-cooked indigestible food as predisposing to peptic ulceration. It is only possible to reiterate that such influences may make the subject liable to the onset or recurrence of a peptic ulcer: they are not of the type readily amenable to analysis. Furthermore, too much stress must not be placed on the operation of such adverse influences. Faulty dietetic habits, for instance, may play their part in a few cases in initiating peptic ulceration, but their importance can be over-emphasised.

Many persons take hurried and irregular meals over long periods, and yet remain free from dyspepsia. In those subjects who have a constitutional predisposition to peptic ulcer, a delicate balance probably exists towards the onset of ulcer which can be tipped in an adverse direction by one or more of a multitude of unfavourable environmental factors at any time.

The importance of the environment in the aetiology of peptic ulcer has attracted the attention of many authors. Early in the century mouth sepsis and respiratory infections were held to favour the development of ulcers. Little is heard of such claims nowadays. More recently Emery and Monroe (1935) have reported the results of a study of possible exciting factors. No cause for the onset of the ulcer could be found in 40 per cent of their patients, but fatigue was considered to have been provocative in 26 per cent, and emotional upsets in a further 20 per cent. Currently, great emphasis has been placed on the close relation between the emotions and gastric function. However, when the literature is reviewed, it is impossible not to be impressed by our real lack of knowledge of the part played by the environment. For

decades, as part of their medical treatment, patients have been advised to take bland, regular meals, cultivate a calm mental outlook, and practise strict moderation in alcohol and tobacco consumption. But to what purpose? Peptic ulcer treated medically is known to have a relapse rate of at least 50 per cent within 5 years (Ivy et al. 1950), and the operation of partial gastrectomy (which implies failure of medical treatment) is being carried out on a continually increasing scale. It is not surprising that some clinicians, becoming dissatisfied with the results of orthodox conservative treatment are willing to resort to any expedient, no matter how fanciful, in the hope of giving lasting relief to their patients. At present cabbage-water and gastro-intestinal extracts have their advocates. These substances, like many others, are likely soon to be discarded and forgotten.

#### The Rôle of the Emotions.

The emotional response of the individual to his environment, rather than the environment itself, is now held to play an important rôle in

the pathogenesis of ulcer. The abdomen has been described as " the sounding-board of the emotions", and both clinical studies and experimental observations have demonstrated a close relationship between emotional factors and alimentary tract function. Indeed, most gastroenterologists would be prepared to classify peptic ulcer as a psychosomatic disorder. According to the psychosomatic hypothesis, peptic ulceration results from continued emotional tensions, conscious or unconscious, accompanied by hypothalamic excitation which, in subjects of a particular temperament and constitution, leads to excessive vagal stimulation producing gastroduodenal hypersecretion, hypermotility and congestion; and finally to localised areas of mucosal ischaemia which, acted on by acid gastric secretions for a sufficiently long period, eventually give rise to erosions and chronic ulceration. The literature has been summarised by several authors, notably Miller (1948), while the classical studies of Wolf and Wolff (1942) on a second Alexis St. Martin are well known. Much of the evidence is circumstantial, but it does indicate that psychological factors play a part in initiating the onset or recurrence of peptic ulcer, and psychic trauma must be regarded as a probable

excitatory cause of peptic ulcer in ulcer-susceptible persons. However, since peptic ulcer can still occur when the vagus and splanchnic nerves have been cut (Ivy et al., 1950), the emotional factors though excitatory may not be the basic cause of peptic ulcer. In this series no attempt was made to investigate the emotional background of the 200 subjects studied, as it was considered that this aspect of the problem is properly the province of the trained psychiatrist. Careful psychosomatic studies have already been made, notably by Davis and Wilson (1937), who found a marked emotional component in 84 per cent of their 205 ulcer patients; they describe the ulcer patient as being characteristically irritable, aggressively alert and self-driving.

#### The Rôle of Diet.

Much doubt and difficulty has always been experienced in evaluating the factors which aggravate or predispose to peptic ulcer, and even long-held views on the value of certain medical measures have not escaped criticism. It is not surprising, therefore, that no clear correlation between faulty dietary habits and the onset of the disease has been proved to exist. On the one hand, it is common knowledge that many persons



consume irregular meals of indigestible type over long periods without developing an ulcer. On the other hand, there is no criterion by which unsatisfactory dietary habits can be judged. Also, some subjects will take indigestible food at regular intervals, and vice versa, while in other cases the dietary habits may vary from time to time. The 200 subjects of the series investigated were questioned regarding the type of food and regularity of meals obtaining at the time when ulcer symptoms first appeared. At the onset of the disease, dietary habits were judged to have been good in 124 subjects and bad in the remaining 76. These figures represent only personal impressions, but if they are accepted it is clear that diet does not play a decisive rôle in the causation of peptic ulcer. In this connection the 100 members of the control series cannot be used for comparative purposes. No less than 43 of them were housewives, as compared with only 29 in the major series, and the housewife has much greater opportunities for obtaining regular, digestible meals than any group of male subjects.

Since it is so difficult to judge the importance of the many factors in the environment which may predispose to ulcer, in this work attention has been

concentrated on the three which most readily lend themselves to analysis. They are :-

- A. Occupation
- B. Alcohol Consumption
- C. Tobacco Consumption.

Section A.

Occupation.

In the search for environmental factors which might be significant in predisposing to peptic ulcer much emphasis has been laid on the presumed increased rush and stress of modern life. Urban rather than rural communities might be expected to suffer from the adverse effects of such stresses, and in fact Morris and Titmuss (1944) have succeeded in showing that the mortality rates from peptic ulcer are different in town and country. Having analysed the Registrar-General's mortality statistics and compared the deaths from peptic ulcer in the period 1928-30 with the census populations for 1931, they found a progressive increase from rural districts, through county boroughs, to the County of London. The mortality rates for men over 34 years in the County of London were about 75 per cent more than those in the rural areas. These figures can be explained in one of several ways.

A patient, though domiciled in the country, may die in an urban hospital. Again, diagnosis may be more accurate in the large towns. Nevertheless, they can also be used to support the contention that modern civilisation is to blame for the increased incidence of ulcer. If this view is correct, the possibility exists that occupational factors, arising from modern methods in a wide range of trades and professions, may be of importance. Such factors might operate in a number of ways. Some occupations might entail working with chemical or other agents potentially injurious to the gastroduodenal mucosa; others might interfere with the normal processes of digestion by involving night work, shift work or irregular meal hours. Finally, on the basis of the psychosomatic theory of ulcer genesis, peptic ulcers might be more liable to occur in jobs which caused anxiety or resentment, or where heavy responsibility had to be undertaken.

Soon after peptic ulcer was firmly established as a clinical entity, it was held that the disease was more common in cooks and cobblers. These occupations are no longer considered unduly hazardous in this respect. Since then, extensive investigations of many occupations, involving large series of cases, have only succeeded in demonstrating that peptic ulcers

occur in men doing all types of work, and that the disease is not an occupational one in the absolute sense of the term (Hurst and Stewart, 1929; Alsted, 1942; Thre and Muller 1943). However, the possibility remains that environmental factors, due to the type of occupation, may make peptic ulcer more liable to occur in some jobs than in others. To obtain further information on the subject, Doll, Avery Jones and Buckatzsch (1951) have made a survey in Greater London with the object of determining the incidence of peptic ulcer in the population there, and of estimating the importance of occupational factors in the aetiology of the disease. Their investigation, which is a model of painstaking and accurate field research work, involved the interviewing of 6,047 men and women employed in a variety of trades and professions. A significantly high incidence of ulcers was found among doctors, business executives and foremen. Among agricultural workers and sedentary clerical workers the incidence was lower than expected. Contrary to previous opinion (Hill, 1937; Avery, 1940), an abnormal incidence of ulcers was not observed among bus drivers and conductors. The authors were able to collect some evidence about the underlying factors which might be responsible for the production of occupational differences.

Irregularity of meals and shift work were not considered to have exerted any harmful effects, but anxiety over work was a frequent finding; it was pointed out that both duodenal ulcers and anxiety over work are commonly associated with a particular type of personality.

In Scotland our knowledge of occupational differences in the incidence of peptic ulcer is extremely meagre. Only one publication contains any information on the subject. The Department of Health for Scotland (1935) has analysed insurance certificates for the whole of Scotland, and compared the results for the years 1930-33 with the population of insured persons given by the census of 1931. In this way it has been shown that, as compared with men in other occupations, Scottish miners and fishermen have a high incidence of ulcers (Tables 9 and 10). Ayrshire contains appreciable numbers of men engaged in both occupations. There are known to be over 12,000 miners in Ayrshire (Hospital and Community 2, 1949), and my own estimate of the numbers of fishermen in the county is approximately 350. Many local practitioners would be prepared to record an opinion that peptic ulcer occurs with undue frequency in their patients who are miners or fishermen, but such clinical impressions

can be misleading. It was open to the present author to carry out a field study into the ulcer incidence in either occupational group. Only in this way can the occupational incidence be assessed with any degree of precision. Estimates obtained from analysis of mortality statistics, hospital records and insurance certificates all permit a wide margin of error, and are liable to serious objections. In practice it is necessary to interview a number of the men engaged in any specific occupation, and make personal clinical diagnoses. Miners, although more numerous than fishermen, were not found to be a suitable group for ulcer incidence assessment by a solitary investigator. They are difficult to interview, being inaccessible while at the coal face; at other times they are travelling to or from work, resting or engaging in recreation. At least a quarter of the miners at any pit will be employed at night work, thus adding another obstacle to the would-be interrogator. Fishermen, on the other hand, present a more straightforward problem in respect of facilities for interview. When not at sea, they can readily be found in or near their boats, and they live in small compact communities of known size. The aim of the study about to be reported, therefore, has been to obtain information concerning

Table 9.

Incidence of peptic ulcer among miners and other workers in various parts of Scotland (Department of Health for Scotland, 1935).

Reproduced with permission from M.R.C. Report No. 276

Area	Annual number of cases of incapacity due to peptic ulcer per 1,000 men.	
	Miners	Other workers
Ayrshire	2.86	2.40
Lanarkshire	2.62	2.51
Fife	3.78	2.99
W. Midlothian and Stirling	5.32	2.19
E. Midlothian and Midlothian	3.15	2.71
All Scotland	3.37	2.71

Table 10.

Incidence of peptic ulcer among various occupations in Scotland  
(Department of Health for Scotland, 1935). Reproduced with permission  
from M.R.C. Report No. 276.

Occupation	Annual No. of Cases of Incapacity due to Peptic Ulcer per 1,000 men.
Fishermen	3.67
Gardeners	2.16
Foresters	1.74
Shepherds	1.94
Other farm servants	2.90
All agriculture and fishing	2.55
All Scotland	2.79



the incidence of peptic ulcer among a group of Ayrshire seine-net fishermen. At the same time the opportunity has been taken to investigate, so far as is possible, any likely causative factors.

(Tables 9 and 10 near here) .

#### Preliminary Material.

The enquiry was confined to the fishing village of Dunure, and all the fishermen employed there in that occupation were interrogated. Dunure is situated on the Ayrshire coast 39 miles south of Glasgow. The estimated present population is 550. There has been a fishing community at Dunure for over 200 years; examination of old parochial registers shows the first recorded entry with a "Fishertoun" ( i.e. Dunure) address to refer to the baptism of a child there on 21st February, 1712. Until comparatively recent years the rate of intermarriage was high; transport facilities were minimal and the community was a relatively closed one. Evidence of a high intermarriage rate among generations of former inhabitants is still available. Five common surnames were shared by 40 of the 77 men interviewed. No death from peptic ulcer or its complications is officially recorded as having occurred in this village within the last 5 years;

this would indicate that peptic ulcer is an uncommon cause of death among fishermen, and the Annual Report of the Registrar-General for Scotland (1936) is confirmatory. It reveals that, in the years 1930-32, only 26 fishermen in Scotland died from a peptic ulcer, while 412 succumbed from cardiovascular disease: the latter is by far the most important cause of death in these men.

#### Methods and Results.

The 77 fishermen of Dunure were interviewed personally and a standard questionnaire completed for each man. Advance publicity and previous acquaintance with some of the subjects simplified the task considerably and ensured a high degree of cooperation. Each interview lasted approximately 15 minutes. It was usually conducted in the open air and physical examination was not attempted. A full clinical history was obtained relating to any dyspepsia which had been experienced, and details of its nature, severity and duration were recorded at length. In addition to the age of the subject and the length of time he had spent in his employment, note was also made of the average daily consumption of alcohol and tobacco. The family history was elicited with special reference to dyspepsia of ulcer type. The

Table 11.

Site of ulcer, and method of confirmation of diagnosis, in 10 peptic ulcer subjects from a group of 77 fishermen.

Subject	Site of ulcer.	Method of confirmation of diagnosis.
J. L.	Gastric	Ba. Meal Operation
J. G.	Gastric	Ba. Meal
W. G.	Duodenal	Operation
W. McC.	Duodenal	Operation
R. M.	Duodenal	Operation
A. R.	Duodenal	Operation
J. McC.	Duodenal	Ba. Meal
W. McC.	Duodenal	Ba. Meal
H. E.	Duodenal	Ba. Meal
J. D.	Duodenal	Ba. Meal

subjects were classified into the following categories, the criteria for which are as stated:-

No Dyspepsia .

There were either no stomach symptoms, or only occasional indigestion associated with dietary indiscretions was admitted. The sole victim of seasickness is also included within this category, since he was free from seasickness while ashore. 58 subjects were thus classified.

Peptic Ulcer.

A history of any one or more of the following was accepted as evidence of the presence of a healed or active ulcer:-

- (1) Perforation, with operative closure.
- (2) Gastro-enterostomy or partial gastrectomy.
- (3) Barium meal said to have shown an ulcer.
- (4) Gross upper alimentary haemorrhage without other obvious cause (none of the subjects admitted such an incident).

In all cases the statements obtained were verified by a study of hospital records. The ulcers were classified by site as shown in Table 11, two being gastric and eight duodenal (Table 11 near here) . 10 subjects (13 per cent) fulfilled these requirements.

Table 12.

Classification by age group of 77 fishermen, including those who had suffered from peptic ulcer.

Age (years)	All Fishermen.	Ulcer Cases.	
		Proved	Presumptive
14 -	4		
20 -	8		1
25 -	12	3	
35 -	27	2	3
45 -	21	5	2
55 +	5		
TOTAL	77	16	

### Presumptive Peptic Ulcer.

A history was obtained which, from its features, was strongly suggestive of recent peptic ulceration.

A barium meal examination was offered to these subjects, but the nature of their employment did not permit them to accept.

6 men (7.3 per cent) are included in this group.

### Other Dyspepsia.

Dyspepsia was admitted, but its features were not those of peptic ulcer. Of the three subjects in this category, one had had the stomach extensively investigated with entirely negative results, a second had symptoms suggestive of disease of the appendix, while the third appeared to suffer from chronic gall-bladder dysfunction.

All the fishermen, and those suffering from peptic ulcer, have been classified by age groups in Table 12. The average age of the whole group of men was 38.6 years: that of the proved ulcer subjects was 41.4 years. (Table 12 near here).

The method of investigation described is subject to certain errors and limitations. On the one hand there was no lack of cooperation, the whole sample was interviewed, and an attempt was made to eliminate personal bias in favour of a positive

diagnosis. On the other hand the sample is a relatively small one. To obtain an assessment of the incidence of ulcer applicable to all Scottish fishermen which at the same time would be of strict statistical significance, it would have been necessary to interview many more subjects. Such a widespread enquiry, though obviously desirable, was not within the scope of this investigation for two reasons. Firstly, one investigator working alone could not interview a large body of men sparsely scattered along the coastline, and at the same time hope to complete the survey within a reasonable period. Secondly, it was thought that hereditary factors of importance in the causation of peptic ulcer might be apparent in the relatively isolated type of community studied. It should also be noted that an attempt to estimate the incidence of peptic ulcer at any given time is made especially difficult by the nature of the disease itself. In many cases attacks of severe dyspepsia, associated with active ulceration, are separated by relatively long asymptomatic periods during which healing of the ulcer may be assumed. Further, it is impossible to be sure clinically that an ulcer has or has not healed. In this series an arbitrary limit has been set concerning the relation of time to the

incidence of dyspepsia. All subjects free from symptoms for 15 or more years have been classified as "No Dyspepsia" irrespective of their previous history. A final limitation in estimation ulcer incidence is that victims of severe dyspepsia might have been forced in consequence to abandon their employment; thus they would escape inclusion in the series, with artificial depression in the rate of incidence. No accurate estimation could be made of the numbers of such persons, but the enquiries made suggested that it was very small.

### Discussion.

#### (a) Incidence.

Of the 77 fishermen studied, it will be observed that 13 per cent were proved to have had an active peptic ulcer within the past 15 years. In a further 7.3 per cent there was presumptive evidence of a recent active ulcer. Such an incidence of ulcer in the fishermen of this community is impressive, even when allowance is made for the facts that the incidence of ulcer is unknown both in the population of Scotland and in the main occupational groups of which it is largely composed. No strictly comparable figures from other countries are available, but the most useful are those of Doll, Avery Jones and



Buckatzsch (1951). In men of 35 - 44 years living in and around London their estimate of ulcer incidence was 7 per cent.

One other author has studied the incidence of peptic ulcer among fishermen. Schanke (1946), working from Stokmarknes Hospital in northern Norway, found that peptic ulcers among local fishermen were unduly common. Duodenal ulcers were not found more frequently among fishermen than among men in other occupations, but gastric ulcers were significantly more common; they numbered 10.7 cases per 1,000, as against 5.6 per 1,000 in other occupations. The results observed in the present series, as seen in Table 11, are quite different: duodenal ulcers outnumbered gastric ulcers by 4 to 1. These results suggest that, if a true excess of ulcers occurs among Scottish fishermen, the site distribution merely reflects that already in existence among peptic ulcer subjects in Scotland. The Scottish mortality figures for 1947 (Doll, 1952) indicate that under the age of 45 years duodenal ulcers are twice as common in Scotland as in England and Wales. The preponderance, therefore, of duodenal as opposed to gastric ulcers among the fishermen probably does not differ greatly from what might be expected among men in any other occupation in Scotland. In

short, it is concluded that there is strong evidence to suggest an excessive incidence of ulcers among Scottish fishermen, but the occupation per se is believed to play little or no part in deciding at what site the ulcer will develop.

(b) Environment.

The reasons for such an excessive incidence are obscure. Both hereditary and environmental influences may be of causative importance. From the aspect of environment, and in accordance with accepted medical teaching, the nature of the employment might be incriminated. Fishermen are subjected to physical exposure, mental strain, long period of hard physical exertion with but little sleep, and take hurried and poorly prepared meals at very irregular intervals. Such conditions may play some part in predisposing to the disease, but they cannot be further analysed. However, within certain limits, an estimate of alcohol and tobacco consumption can be made. Since these substances are widely believed to be of importance either in causing ulcers, or in preventing the healing of established ulcers, an attempt has been made to form such an estimate by enquiry among the group of men studied. The rôle of alcohol and tobacco in

the aetiology of peptic ulcer is discussed subsequently at length in Sections B. and C.

Alcohol consumption was found to be low. Of the 77 men interrogated, 59 were either total abstainers or only indulged in strict moderation on festive occasions. In addition, the consumption of the ulcer subjects could not be judged excessive by any reasonable standard. Taking the group as a whole, no more alcohol than that present in one pint of beer or its equivalent was consumed weekly. It is perhaps a truism to add that, where alcoholic refreshments are concerned, both inclination and opportunity must be present. Fishing craft rarely carry alcoholic beverages in any form on board, and there are no licensed premises in Dunure.

Daily tobacco consumption readily lends itself to estimation, and each subject was also questioned on this point. The proved ulcer subjects smoked an average of 19 cigarettes per day, while the consumption of the whole group averaged 19.5 cigarettes daily (in this Section and subsequently the conversion factor of "1 oz. of tobacco a week = 4 cigarettes a day" has been used : Doll and Hill, 1950). Each day 31 per cent of the men smoked 25 or more cigarettes. These results suggest that the fishermen

Table 13.

Smoking habits of 77 fishermen, including ulcer and non-dyspeptic subjects.

	No. of fishermen.	No. smoking 25 or more cigarettes daily.
No Dyspepsia	58	19
Proved Ulcer	10	4
Presumptive Ulcer	6	2

of Dunure are unduly heavy smokers, but no information is available at present regarding the smoking habits of Scotsmen in other occupations. However, figures can be obtained for purposes of comparison from two sources. In Chapter 2 of this work, 200 proved ulcer cases are analysed. Of the first 77 men in this series, 14.3 per cent smoked 25 or more cigarettes per day. Again, Doll and Hill (1950) have carried out in London an enquiry into the importance of tobacco in the aetiology of bronchial carcinoma. Of their 622 male control subjects, who did not suffer from the disease, 13.5 per cent smoked 25 or more cigarettes daily. It will be observed, therefore, that the percentage of fishermen who were heavy smokers was at least double that in the other two groups. Further analysis, however, reveals no significant correlation between heavy tobacco consumption among the fishermen and the presence of peptic ulcers. From Table 13 it will be noted that heavy smokers were distributed in similar proportions of almost precisely one-third between the non-dyspeptic and the ulcer subjects. In brief, the fishermen as a group were heavy smokers, but tobacco consumption was as great among the healthy fishermen as in those who had ulcers. (Table 13 near here).

It is concluded, therefore, that excessive consumption of alcohol and tobacco played no significant rôle in the aetiology of peptic ulcer as observed in the group of fishermen studied.

(c) Heredity.

It has for long been noticed that relatives of peptic ulcer patients often have ulcers or complain of dyspeptic symptoms, and some families with a remarkable number of dyspeptics in them have been recorded. It has not been possible, however, to conclude from this that peptic ulcers are hereditary, for they are so common that it is by no means unlikely for several members of a family to be affected. Recently, in this work and elsewhere, it has been possible to overcome this difficulty, and the results confirm that there is a distinct hereditary factor. It seems probable that ulcers occur about twice as often in ulcer families as would be expected. What is inherited appears to be the susceptibility to have an ulcer, but whether one actually develops must be largely dependent on the conditions to which the subject is exposed.

In this series a history of dyspepsia of ulcer type was obtained affecting 43 relatives of the 77 subjects studied, and in 16 of these relatives there

was strong presumptive evidence of a peptic ulcer (e.g. history of gastric operation or barium meal). The relatives mentioned were confined to the parental generation, siblings and children of the fishermen interviewed. The series was not sufficiently large, however, to permit a satisfactory comparison to be made between the incidence of ulcers in relatives of dyspeptic as opposed to non-dyspeptic subjects.

The importance of the hereditary factor in the causation of peptic ulcer is extremely difficult to estimate. The peculiar problems inherent in a human genetic study of such a disease add to the complexities of a subject only the fringe of which has, as yet, been explored. Nevertheless, it is reasonable to assume that the inherited factor is either a recessive or dominant gene or gene-complex. Recessive genes in man will be detected most readily in communities which show a high degree of inbreeding, and attention has been drawn to the fact that, until recently, the population of Dunure was relatively inbred. At present inbreeding in this community is steadily decreasing, while outbreeding progressively increases. It might therefore be expected that, if a harmful recessive gene of importance in causing peptic ulcer were present in earlier members of the community, it would spread widely.

A similar spreading process would also occur in other communities. At the same time, since two identical harmful recessive genes would be much less likely to join in one human individual, a fall in the incidence of a disease in which heredity played a major rôle might be expected. This fall would continue in the presence of an expanding mating system. By contrast, the incidence of peptic ulcer in this country is increasing, and there is no reason to suppose that Dunure is an exception in this respect. It must be concluded, therefore, that the gene or gene-complex concerned is of the dominant type with a low rate of expression, readily operative in the aetiology of peptic ulcer only when environmental factors strongly favour the onset of the disease.

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#### SECTION B.

#### ALCOHOL CONSUMPTION.

It is customary to forbid ulcer patients to take alcohol in any form, and with justification. Alcohol, unless taken well diluted and in strict moderation, acts as a gastric irritant. Using the gastroscope, it can be shown that about 50 per cent



of chronic alcoholics have gastritis (Ivy et al. 1950), though the achlorhydria which is so often found in this condition may account for the fact that the incidence of peptic ulcers in such persons is not increased. The drug is also a powerful stimulant of gastric secretion. Indeed, it is used instead of gruel in some centres when carrying out a fractional test meal; 50 to 100 ml. of a 7 per cent solution is the customary amount given. Nearly all clinicians are at one in warning their ulcer patients against the use of alcohol, but few have attempted to investigate its possible rôle in ulcer pathogenesis. Redwitz and Fuss (1928) could not find any direct aetiological connection between ulcers and the consumption of alcohol, but recorded evidence which suggests that alcohol may provoke recurrence of ulcers in some patients.

Since alcohol has long been considered to be a possible predisposing factor in the causation of peptic ulcer, an enquiry was carried out into the customary alcoholic habits of the male subjects among the 200 cases described in chapter 2, and also into those of 57 male controls. Female patients are excluded, since in the present series they were found to be uniformly abstemious.

The alcohol consumption of the 171 proved ulcer cases in males was compared with that in 57 non-dyspeptic male controls, and each group was divided into three subdivisions, depending on whether the average weekly alcohol consumption was "excessive", "moderate" or "nil". Although these standards are to some extent self-explanatory, they cannot be defined with accuracy. The habits of the habitual drinker vary much from time to time, not only in the volume consumed, but in the type of beverage and its alcohol content, which may even be different in various localities. The cases have therefore been classified by the author in a somewhat arbitrary fashion which at least has the merit of applying to ulcer and non-ulcer cases alike. Those subjects who had an alcohol consumption of "nil" were either strict teetotallers or indulged rarely and in strict moderation on festive occasions. The alcoholic habits of the ulcer patients were those in effect at the time when symptoms of dyspepsia first appeared, and before the consumption had been changed by the physician in charge, or by the patient on his own initiative.

Table 14.

Alcohol consumption of 171 male ulcer subjects, and of 57 male control subjects.

Alcoholic Habits	No. of ulcer patients.	No. of control subjects.
"Excessive"	13 ( 8%)	9 (16%)
"Moderate"	58 (34%)	16 (28%)
" Nil"	100 (58%)	32 (56%)
TOTAL	171	57

The results are shown in Table 14, in which the percentages of ulcer patients and controls falling into each of the three main categories are shown. It will be observed that there was a deficiency of heavy drinkers in the ulcer group, and that there was no significant difference between the numbers of moderate and non-drinkers in the two classes. It is concluded, therefore, that while the consumption of alcohol may play some part in delaying the healing of established ulcers, it has no significant rôle in predisposing to the onset of the disease. (Table 14 near here).

### SECTION C.

#### TOBACCO CONSUMPTION.

The effect of smoking on gastric function is a subject of great importance, because it has long been traditional to urge the patient with a peptic ulcer to abstain. Unfortunately, few subjects have been confused by so many poor observations and by such wild generalisations. Authoritative medical opinion varies from a belief that smoking may cause peptic ulcer, to a conviction that it has nothing to do with the onset or course of the disease.

Smoking a cigarette inhibits gastric motility and hunger contractions (Carlson and Lewis, 1914), but the emptying time of the stomach after a meal is unaltered (Schnedorf and Ivy 1939); it is thought that the increased appetite noted by many after renouncing tobacco may be due to removal of the inhibitory influence of tobacco on gastric motility. These effects are probably mediated reflexly, for they cannot be reproduced after injection of nicotine into experimental animals. Dogs can inhale tobacco smoke over long periods without any alimentary lesions appearing, but if histamine injections are also given most of the animals will develop duodenal ulcers and erosions (Toon, Cross and Wangensteen, 1951). In man, smoking has not been found to cause hypersecretion of acid-pepsin (Ivy et al., 1950). Wolf and Wolff (1943) watched the behaviour of the stomach in their patient Tom, who had a large gastric fistula. When smoking evoked pleasant sensations, there was no change in gastric motility, secretion or vascularity. When he smoked a cigarette without any real desire to do so, there were observed slight nausea, mucosal pallor and gastric anacidity and amotility; these changes were common to the sensation of nausea however produced.

It will be noted that these physiological observations provide no theoretical justification for advising the patient with peptic ulcer to stop smoking. None the less, many physicians are convinced that tobacco has a deleterious effect on the disease. Bennett (1925) states that, in his view, it is rare to discover a duodenal ulcer in a non-smoker, and Price (1947) is of the opinion that the tendency to develop a duodenal ulcer is increased by excessive smoking. Tyrell-Gray (1924) analysed a series of men who had a duodenal ulcer, and found that 96 per cent were smokers; tobacco consumption was considered to be "excessive" in 29 per cent, "heavy" in 31 per cent and "mild" in 40 per cent. These authors have helped to crystallise an opinion, long held, that the patient with a peptic ulcer is often a heavy smoker ( e.g. Bockus, 1944). Hurst and Stewart (1929), in particular, hold decided views on this subject. After stating that " most people with duodenal ulcer have smoked excessively for many years", they continue"-----  
The liability to develop a duodenal ulcer is increased by excessive smoking, and when an ulcer has formed its tendency to heal is reduced and its tendency to cause pain is exaggerated. Nearly every ulcer patient is aware that his symptoms are

aggravated by smoking, and may reduce his consumption of tobacco on his own initiative. A return of pain in a quiescent ulcer or a relapse after an ulcer has healed may follow a period of excessive smoking, and one reason why worry aggravates the symptoms of ulcer is that it is so often an excuse for over-indulgence in tobacco". It should also be noted that some patients are said to obtain relief from their dyspeptic symptoms on avoiding tobacco (Wagner, 1924 : Bockus, 1944: Schindler, 1947). Recently Batterman and Ehrenfeld (1948) showed that the effectiveness of the antacid treatment of their peptic ulcer patients was decreased by smoking. It is still unknown, however, how these effects are mediated.

It may be thought from the foregoing that a strong case exists for urging the ulcer patient to stop smoking. However, such an impression would be incorrect. It is possible that the opinions of some of the authorities quoted may have been based, to a certain extent, on that notoriously dangerous guide the "clinical impression". While it may be true to say that the view adopted by the average doctor tends to be dictated rather by the number of cigarettes he smokes himself than by a profound knowledge of the pharmacology of tobacco, it must also be admitted that those who do not advise restraint in the use of

tobacco to their ulcer patients can point to evidence which supports their opinions. A careful follow-up of a group of patients by Jamieson, Illingworth and Scott (1946) revealed no correlation between alterations in tobacco consumption and variations in the severity of ulcer symptoms. Further, Trowell (1934) has concluded from a personal survey that men with chronic duodenal ulcer do not smoke, on an average, more than healthy men of the same age, although twice as many inhale. The significance of this last observation is obscure. Most cigarette smokers would agree that the pleasurable effects of smoking are enhanced by inhalation, and in these days of high tobacco prices there must be very few cigarette smokers who do not inhale. Information is lacking on whether, except following deep inhalation, tobacco smoke normally reaches the area of maximal absorptive capacity - the terminal lung unit; if it does so it will have by then been diluted fifteenfold by the air in the respiratory passages (Fabricant, 1946). The degree of importance which should be attached to Trowell's results on this point is therefore difficult to assess. Since these results are based on the study of a small series of only 50 cases, his observations on the subject of



inhalation must be regarded with some reserve.

When the mass of conflicting opinions and inconclusive experimental work is reviewed, it is clear that a final answer to the vexed question of the importance of tobacco consumption in the peptic ulcer subject is likely to be obtained from research directed along one or both of two main channels.

These are :-

1. Pharmacological Studies.

Further experimental evidence derived from a large series of cases is required regarding the response of gastric motility, vascularity and acid-pepsin secretion to smoking, both in ulcer and in non-dyspeptic subjects. As the present evidence is inconclusive, there is every indication that additional research (even should it prove negative) would be instructive in this field. At least part of the work might be conducted along the lines suggested in a recent publication (Melrose, 1951), in which was described the action on gastric motility of one of the drugs currently used in the treatment of peptic ulcer.

2. Statistical Studies.

Reference has been made to those studies which have already been conducted (Trowell, 1934:

Jamieson, Illingworth and Scott, 1946) and, to the author's knowledge, the results of no similar investigations have been recorded in the world literature. Even though the few statistical enquiries which have been published to date tend to minimise or negate smoking as a factor in causing ulcer or in aggravating ulcer symptoms, it would be incorrect to regard them as conclusive. It may or may not be true that the proportion of smokers among ulcer patients is no greater than the proportion of smokers among the population at large, but it is still possible that some ulcer patients are particularly susceptible to the effects of smoking. As there is such a lack of statistical evidence in this field, it was decided to carry out a personal enquiry into the smoking habits of ulcer and non-dyspeptic subjects in this area, and the remainder of this section is devoted to the recording of the results of such an investigation.

An ancillary line of enquiry would be therapeutic. The effects of stopping smoking on ulcer symptoms would constitute a "reversed therapeutic trial". One observer (Doll, 1952) has already considered carrying out such a trial on a group of ulcer patients. It is doubtful whether such a trial would yield decisive results. The factors

which aggravate or ameliorate ulcer symptoms are numerous, and it is possible that all of them are not yet known. Any conclusions drawn from such a study would require to be accepted with considerable caution.

#### Material and Methods.

In this section a statistical enquiry has been made into the smoking habits of two groups of men - 161 male subjects suffering from a proved duodenal ulcer, and 271 non-dyspeptic male controls. The 161 ulcer patients are a portion of the group of 200 cases described and analysed in Chapter Two. The criteria for proof of the presence of a duodenal ulcer have been set out there. In each case a record was made of the daily quantity of tobacco smoked at the time of onset of symptoms, the amount being expressed in the form of numbers of cigarettes ( the usual conversion factor from pipe tobacco to cigarettes was employed). The control group was a mixed sample of the local male population. One hundred were non-dyspeptic male hospital patients, whose present daily tobacco consumption was noted by me. However , a difficulty arose in respect of the control subjects; the supply of hospital patients available for interview was strictly limited. Also, it was desirable that the

Table 15.

Classification of disease conditions by system from which 271 control subjects were suffering.

System	No. of Subjects
Musculoskeletal	40
Respiratory .	60
Cardiovascular	46
Blood, Allergic, Endocrine	15
Alimentary (excluding peptic ulcer)	13
Urogenital	6
Central Nervous, Eyes, E.N.T.	22
Trauma and Sepsis	33
Neoplasia	4
Functional	11
Miscellaneous, including Skin Disease	21
TOTAL	271

male control subjects should either be healthy persons or, if not, should represent as broad a sample of the local male population as possible. Interviewing large numbers of healthy men about their smoking habits was not found to be a practicable procedure, but an acceptable alternative group consisted of local men who were attending the surgery of a local general practitioner for the treatment of ailments which were usually of a minor nature. I am therefore indebted to Dr. A.W. Paterson, an Ayr practitioner, for supplying me with data on the daily tobacco consumption of the remainder of the 271 control subjects. In Table 15 are displayed briefly the main disease conditions by system from which all the control subjects were suffering. (Table 15 near here).

The merits, demerits and limitations of the method may now be assessed. It should first be noted that the daily number of cigarettes smoked by the ulcer patients was that being consumed at the actual time of first onset of symptoms. The distinction between present and past consumption is important, as some ulcer victims come to limit their tobacco consumption either voluntarily or on medical advice. From a study of previous literature it appears likely that some authors have not made allowance for this fact. However,

a difficulty is evident when the results are examined, for one is then comparing what the tobacco consumption was in the two groups at two quite separate points in time. The error, if any, is inherent in the method and cannot be overcome when investigating such a disease as peptic ulcer, which runs a long course, usually of years. Nevertheless, the validity of the results obtained is not affected unless it can be shown that the smoking habits of the community changed during the mean time interval between the two sets of observations. Such a change is not thought to have occurred during the period under review. It will be noted from Table 5 that almost 70 per cent of the ulcer patients had a history of symptoms not exceeding 10 years in duration. During this period no fall in revenue from tobacco taxation has been reported by the Chancellor of the Exchequer. Indeed, in the years of the Second World War, national tobacco consumption reached a new peak.

A further item of note is that the control group was not composed of healthy persons, but consisted of men under medical care. The possibility exists that, due to the nature of their illness (e.g. respiratory disease), they had voluntarily reduced their tobacco consumption below its normal

level. The obstacle was overcome by recording the customary consumption, which was not necessarily identical with that obtaining at the time of interview.

As will be noted from subsequent Tables, the age groupings of the men in the two series of cases were substantially the same. There was a slight preponderance of men in the higher age groups in the control series as compared with the ulcer series. However, as peptic ulcer is a disease condition affecting young and middle-aged rather than elderly men, this was only to be expected.

After the control data had been collected, it was found possible to confirm from an independent source that it provided reliable information on the smoking habits of Scottish men. Recently the Central Office of Information instituted a Social Survey in Scotland and Wales, in the course of which enquiries were made into tobacco consumption among men in both countries. The results have kindly been made available to me, and are summarised with permission in Table 16, which shows the distribution of men in Scotland and Wales by age groups according to the amount smoked. It was not found possible after the investigation was complete to separate the Scottish and Welsh figures. I am assured, however, that the

Table 16.

Distribution of Wives in Scotland and Wales according to amount smoked, by age groups.

From a Social Survey carried out by the Central Office of Information. Reproduced with permission.

Age Group (years)	Most recent amount smoked per day in cigarettes.					TOTAL
	0	1 - 4	5 - 14	15 - 24	25+	
21 - 34	10	1	22	22	4	59
35 - 44	5	1	20	15	3	44
45 - 54	9	1	22	22	4	58
55 - 64	3	1	12	8	0	24
65 - 74	4	3	2	1	1	11
75 +	1	2	6	0	0	9
All Ages	32	9	84	68	12	205



Table 17.

Distribution of 161 Male Duodenal subjects by age groups, according to amount smoked at time of onset of symptoms.

Age Group (years)	Amount smoked per day in cigarettes at time of symptom onset.							TOTAL
	0	1 - 4	5 - 14	15 - 24	25 - 49	50 +		
15 - 24	2	0	7	3	0	1	13	
25 - 34	6	0	10	17	2	1	36	
35 - 44	3	1	17	13	10	0	44	
45 - 54	1	1	16	17	4	1	40	
55 - 64	1	1	5	6	7	0	20	
65 +	1	1	3	3	0	0	8	
ALL AGES	14	4	58	59	23	3	161	

Table 18.

Distribution of 271 Male Control Subjects by age group, according to amount smoked.

Age Group (years)	Amount smoked per day in cigarettes.							TOTAL
	0	1 - 4	5 - 14	15 - 24	25 - 49	50+		
15 - 24	2	1	17	7	1	0	28	
25 - 34	8	2	22	16	2	0	50	
34 - 44	5	1	17	18	4	0	45	
45 - 54	13	0	33	16	6	2	70	
55 - 64	12	4	23	11	4	0	54	
65 +	5	3	10	6	0	0	24	
All Ages	45	11	122	74	17	2	271	

sample for Scotland accounts for two-thirds of the total number (202), and that the average amount smoked was the same in both countries. If Table 16 and 18 are compared it will be observed that the smoking habits of the two groups of men were almost identical. It is claimed, therefore, that the tobacco consumption by age group as expressed in the control series is a truly representative sample of the smoking habits of local men. (Tables 16, 17 and 18 near here) .

### Results.

The results of the survey are shown in Tables 17 and 18. In Table 17 is indicated the amount in cigarettes smoked per day at the onset of symptoms in 161 male proved duodenal ulcer subjects by separate age groups. A similar procedure has been applied in Table 18 to the present tobacco consumption of the 271 male control subjects.

These results were submitted to Dr. Doll of the Medical Research Council's Statistical Research Unit, to whom I am indebted, for an independent opinion, and he confirms that there is an arithmetically significant difference between the two series. There are less non-smokers among the duodenal ulcer patients, and this deficiency is statistically significant

(  $0.001 < P < 0.01$  ). Of those who did smoke, however, the ulcer patients were not found to have smoked more heavily in any age group than the corresponding control subjects.

#### Discussion.

In view of the above findings, it can no longer be confidently maintained that oversmoking plays an important rôle in ulcer genesis, for it has not been possible to show that duodenal ulcer subjects were unduly heavy smokers at the onset of their disease. The fact that it has been demonstrated that there are more smokers among men with duodenal ulcers than among other men does not weaken the validity of the argument against smoking as an exciting cause of ulcers. As is well known, duodenal ulcer most frequently occurs in men of the tense, energetic and ambitious type, and it would be but natural for this kind of man to avail himself of that mental relaxation to be obtained, as many believe, from smoking tobacco. In short, it may be said that the duodenal ulcer subject is more often a smoker than his fellow because of his particular type of personality. On an average, he does not smoke more heavily than other men, and the fact that he is a smoker plays no part which can be ascertained in

deciding whether or not he will develop an ulcer. The results of the present investigation are therefore in accord with those of Trowell (1934) , to whose findings reference at some length has already been made.

## CHAPTER FIVE.

## CONCLUSION.

When considering such a disease as peptic ulcer, about which so little is known with certainty and so much is speculation, it is essential to take a broad view. In this work it has been the aim to examine and investigate in turn certain of those factors which are known or suspected to predispose to the disease. The results obtained from so doing, and the relevant conclusions, may now be reviewed briefly. The literature pertaining to each aspect has been summarised. In Chapter Two peptic ulcer as it affects 200 Ayrshire patients has been analysed in respect of age, sex, social class, site incidence, the incidence and severity of complications and the results of operative treatment. Particular attention has been drawn to alteration in site and general incidence with varying geographical location. The findings in this part of the work differ in few respects from those recorded by previous observers. It was not expected that they would do so. Chapter Two consists, essentially, of an assessment of material as a preliminary to going on to a study of possible predisposing factors. The influence of heredity has been investigated in Chapter Three, where it is

shown that there is a distinct hereditary basis to the disease; among the siblings of ulcer subjects, peptic ulcers were found twice as often as might have been expected. In Chapter Four the importance of occupation and other factors have been investigated. For one Scottish occupation, that of seine-net fishing, the actual incidence of ulcers has been shown to be at least double the expected incidence. Tobacco and alcohol consumption in ulcer subjects have also been investigated, with results which do not support some existing views on their rôle in the causation of the disease. Over-smoking and excessive drinking were found to play no significant part in ulcer genesis, not only among the main group of ulcer subjects, but also among the members of the fishing community. The significance of all these findings has been discussed at length.

As several authors have been at pains to indicate recently ( e.g. Hutchison, 1952), the aetiology of peptic ulcer still remains unknown. Speculation and prophecy on this subject has many dangerous pitfalls. It is possible, however, to indicate one facet of the problem of ulcer genesis which has, hitherto, been much neglected. This is the connection between cerebral and gastric dysfunction. It has long been held that acid-pepsin hypersecretion and

and gastric hypermotility result from vagal overaction which if sufficiently intense and prolonged, may conceivably overcome mucosal resistance and cause the formation of a chronic peptic ulcer. Hence the operation of vagotomy has had its advocates in the surgical treatment of peptic ulcer, especially of the stomal variety. No success has been obtained in attempting to demonstrate vagal overstimulation in ulcer subjects, and due to formidable experimental difficulties it has not been possible to show that such prolonged overaction causes peptic ulcers in healthy persons. The theory of vagal overaction presupposes that abnormal or excessive stimuli, arising in the cerebral cortex of the frontal lobes, are relayed via the hypothalamus to the vagal nuclei, whence they exert their effect on the susceptible end-organ - in this case, the stomach and duodenum. It is of interest to speculate whether, in the patient with the "ulcer-type personality", prolonged psychogenic stimuli with vagal overaction have not been responsible for the development of the disease. There is here a field for further study at once inviting and unexplored. Clinical experience already provides clear evidence of the dramatic association of acute emotional disturbance with the onset of symptoms or relapse in peptic ulcer subjects. For example, acute anxiety has



been noted to precede the complications of haemorrhage or perforation (Davies and Wilson, 1937). It must be admitted, however, that it is the exception rather than the rule to be able to relate emotional catastrophe to the onset of the disease.

Although the relation between psychological disturbance and peptic ulceration remains obscure, that between organic cerebral lesions and the digestive tract is well established. Experimentally, Watts and Fulton (1934) and Davey (1949) have shown that, in monkeys, areas of the frontal lobe cortex exist the stimulation or ablation of which lead to changes in the motility and secretions of the stomach and intestinal tract. Brown-Séguard (1876) reported a perforated gastric ulcer in a dog whose frontal lobes he had cauterised, and Mettler et al. (1936) frequently found gastro-intestinal ulceration in decorticated animals. In man, digestive disturbances are known to occur occasionally after prefrontal leucotomy. Cushing (1932) records a case in which, at post-mortem examination, multiple superficial <sup>0.5x</sup> bleeding stomach ulcers were found; in the brain the remainder of a meningioma, previously removed, was situated in the olfactory groove, together with a large area of softening in the frontal lobe caused by ligation of the anterior communicating cerebral artery. A similar

case is reported by Bodechtel (1935), and Arteta (1951) has recently placed on record two cases in which fatal neoplastic frontal lobe lesions were associated with acute multiple ulceration of the stomach and duodenum. At present three anatomical pathways are accepted as connecting the frontal area to the primary subcortical centres- one to the anterior thalamic nucleus, another to the dorso-medial nucleus of the thalamus, and a third to the hypothalamus (Ward and McCulloch, 1947). Other hypothalamic regulating mechanisms probably exist, and until the anatomical and physiological problems involved are more clearly elucidated. it is likely that the relation between the nature and mode of transmission of nervous stimuli to the stomach on the one hand and gastro-duodenal lesions on the other will continue to be ill-understood.

As Ogilvie (1952) points out in his own trenchant fashion , "all the best people have peptic ulcers. One in every ten adults in Britain is so afflicted. These sufferers are, on the whole the ablest, the most hard-working, and the most conscientious members of the community. Their lives are made miserable and their working efficiency is diminished by pain and indigestion". Peptic ulcer is also one of the twelve diseases most costly to the community. It is manifestly unsatisfactory that so many of the most valuable members of our

population should continue to suffer from a protracted and sometimes disabling disorder. The plea for further research into the unsolved problems of peptic ulcer causation has already been made, and will not be reiterated. Few members of the medical profession seem to find attraction in the unanswered questions of ulcer aetiology, and this may be due to the fact that, in the past, ulcer research has so often yielded disappointing results. Some promising lines of enquiry which might be pursued have been indicated in the present work, of which the physio-pathology of the brain-stomach relationship might well prove to be the most fruitful. Not every aspect of the problem is of equal importance, but each has its place. From the therapeutic aspect it might be thought, for example, that little would be gained from knowing that peptic ulcer has a hereditary basis. However, if the near-relatives of peptic ulcer subjects were aware that they had a certain predisposition to the disease, they would be inclined to seek medical advice early should any dyspepsia supervene; much needless suffering might thus be prevented. Similarly, when the occupational incidence of the disease has been fully worked out, it will be possible to keep peptic ulcer in mind as a cause of any obscure dyspepsias occurring

in certain occupations.

The eminently satisfactory results currently obtained from the operation of partial gastrectomy in the treatment of peptic ulcer naturally do not encourage research into the cause of the disease. Such results, however, should be interpreted, not as an indication for complacency, but as a challenge. When it is necessary to carry out surgical ablation of part of the alimentary canal in order to obtain a cure, such a procedure should be accepted as a confession of failure - failure to find the cause, failure to prevent, and failure to obviate the establishment of chronically- disabling symptoms.

It is a matter for regret that so few centres exist in Scotland where peptic ulcer research can be conducted. With the exception of one Unit in Edinburgh, there are, to the author's knowledge, no wards in any Scottish hospital devoted exclusively to the investigation and treatment of alimentary disorders. This constitutes a grave disadvantage to the surgeon as well as to the physician for, as Ogilvie (1952) remarks, if gastric surgeons were afforded the same privileges as are demanded as a right by their prima-donna colleagues, the mortality rate from partial gastrectomy would probably be nil. When reasonable facilities exist it will be possible to begin

to try to elucidate many of the unsolved but vital problems of a disease the extent and importance of which is gradually gaining fuller recognition.

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Theories of Ulcer Genesis.

1. Intra-gastric or Intra-duodenal.

A. Mucosal Disturbances

- (1) Excessive secretion of acid-pepsin and a deficiency of normal neutralising secretions
- (2) Mechanical factors -
  - (a) Rough food
  - (b) Internal and external pressures of organs and clothing
  - (c) Persistalis
  - (d) Spasm
- (3) Irritants in foods and drinks
- (4) Gastritis and duodemitis
- (5) Inadequate production of mucus
- (6) Natural differences in mucosal susceptibility to acid-pepsin

B. Vascular Disturbances.

- (1) Anatomic vascular defects
  - (a) Relatively poor blood supply to ulcer susceptible sites
  - (b) Tugging on blood vessels
  - (c) Abnormal capillaries
  - (d) Infarction
  - (e) Arteriosclerosis
- (2) Physiological disturbances
  - (a) Vasomotor spasm due to nervous or toxic substances.

## 11. Extragastric and Extraduodenal .

### A. Constitutional Predisposition

- (1) Tendency to excessive secretion
- (2) Tendency to spasm of musculature
- (3) Tendency to vasomotor spasm
- (4) Tendency for stomach and duodenum to be affected deleteriously by emotogenic stimuli

### B. Psychogenic

- (1) Certain emotogenic stimuli causing excessive secretion, excessive motor activity or vascular spasm
- (2) Vagotonic or vegetative nervous imbalance

### C. Infectious or Toxic

- (1) Oral Sepsis
- (2) Foci of infection
- (3) Specific streptococci
- (4) Bacterial toxins
- (5) Tobacco
- (6) Skin burns
- (7) Lymph folliculitis

### D. Allergic

E. Nutritional Deficiency.

- (1) Protein
- (2) Vitamin
- (3) Amino-acid
- (4) Mineral

F. Endocrine Glands.

- (1) Pituitary sex glands
- (2) Gastro-intestinal - enterogastrone and urogastrone

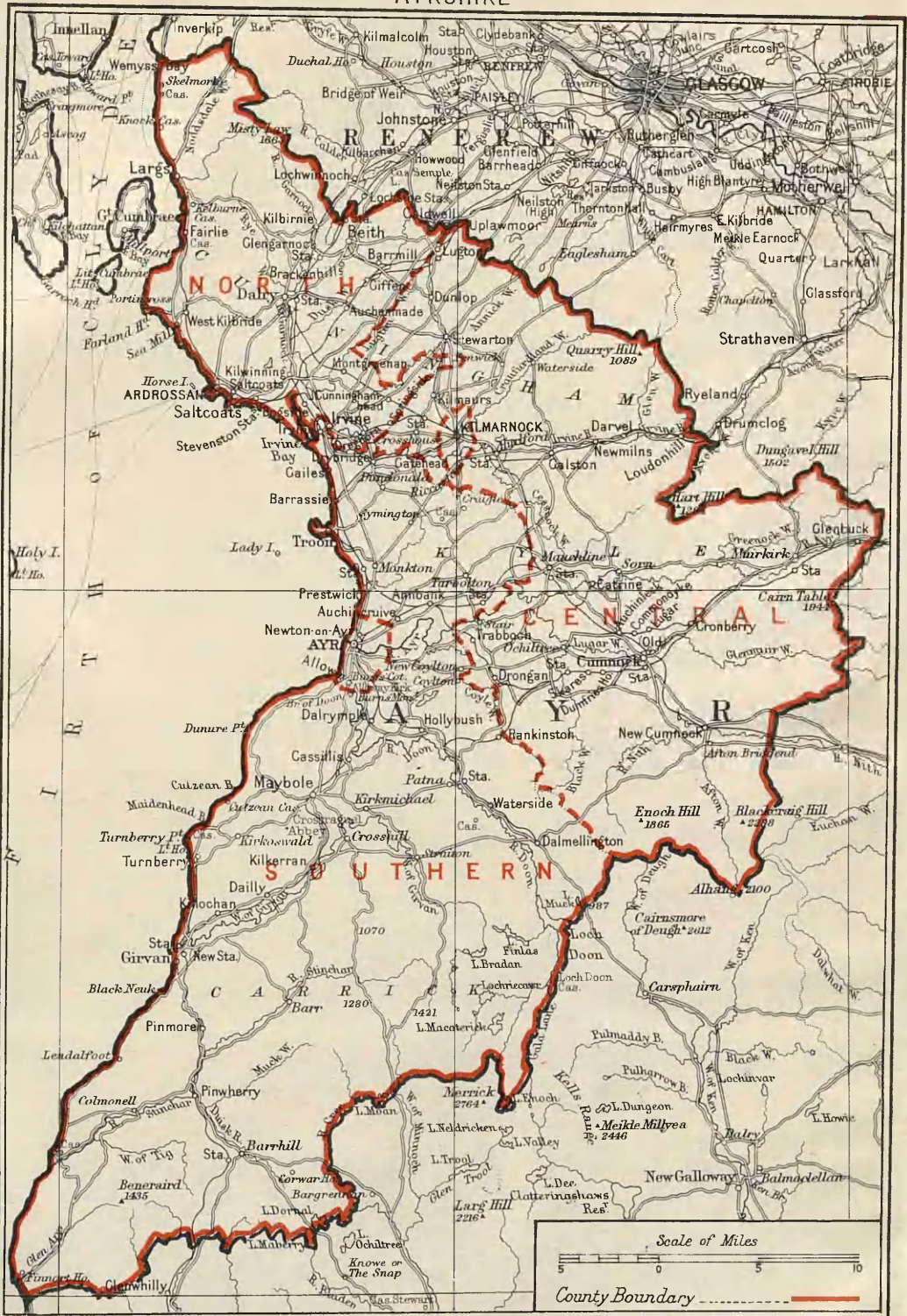
G. Neurotrophic

- (1) Analogous to the buccal aphthous ulcer, or canker sore, which may be vasoneurotic, infectious or allergic in origin.

H. Chronicity Factors

- (1) Mechanical
  - (2) Chemical
  - (3) Mucosal susceptibility
  - (4) Nutritional or reparative.
-

AYRSHIRE



ADDENDUM 3.

<u>NO.</u>	<u>ULCER SERIES</u>	<u>HOSPITAL</u>	<u>DATE</u>
Name .....			I.P/ O.P
Address .....			D.U/ G.U
Age .....	Age at symptom onset .....		SEX .....
Occupation .....		Social Grade .....	
Clinical Diagnosis .....		Marital State .....	M/S/W.
Clinical Details			
Confirmation .....	Ba.Meal .....	Gastroscopy .....	Operation ...
If Operation: .....	Nature .....	Result .....	Sequelae ....

HEREDITY

P.2  
P.1  
F.1  
F.2  
F.3

P

Twinning

ENVIRONMENT

Patient - at time of onset .....

Meals ..... Regular? .....

Type .....

Alcohol .....

Tobacco .....

Domestic Conditions .....

Nervous Factors .....

Affected Relatives.

1

2

3

Domiciled with patient at onset ?

Diet

Alcohol

Tobacco

Present Clinical State

Ulcer Confirmation (if any)

If dead, cause of death.

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Addendum 4.

Distribution of 100 control cases (57 male, 43 female) by means of  
(a) disease groups, and (b) social class.

(a) Disease grouping by affected system

System	No. of Subjects.
Musculoskeletal	4
Respiratory	27
Cardiovascular	26
Haemopoietic	5
Urogenital	2
Endocrine, allergic and metabolic	16
Central Nervous	9
Neoplasia	5
Functional	3
Miscellaneous	3
Total	100.

## (b) Distribution of subjects by Social Class.

Social Class	Number of Subjects
1	0
2	10
3	33
4	19
5	6
6	32
Total	100