Since for many years the intramuscular injection of parental blood has been recommended for the treatment of haemorrhagic disease of the newborn, it appears useful to calculate the frequency with which this procedure might sensitize the infant to the Rh factor. Of the whole population, about 17% are Rh-negative (rr) and 45% heterozygous Rh-positive (Rr). Rh-negative infants can be born to Rh-positive parents in the matings Rr × rr, constituting 15.2%, and Rr × Rr, forming 19.8% of all matings. Therefore, in the first group three out of four and in the second group one out of four of all children will be Rh-negative, so that one or both parents are Rh-positive when the infant is Rh-negative in about 12.5% of all births. It seems that over 6% of all infants could be sensitized by the injection of parental blood.

If all infants were treated thus, about one in three of all Rh-negative females would be sensitized. Fortunately, haemorrhagic disease of the newborn is not common, but, even if it is rare, treatment by injection of parental blood will sometimes result in the appearance of haemolytic disease in the first-born of an Rh-negative mother. Such possible tragedies can be avoided by the use of a vitamin-K analogue, and the use of parental blood in its place will no doubt in future be regarded as a barbarous and unethical procedure.

Conclusion

A history of having received a blood transfusion without special precautions for Rh matching is 18 times more common among mothers of infants suffering from haemolytic disease of the newborn than among unselected patients at the antenatal clinic.

Such transfusion probably causes the disease.

Injection of paternal or maternal blood into an infant without Rh matching would sensitize about one in three of the Rh-negative females at risk.

It is wrong to inject any female with blood from another individual unless either the recipient is known to be Rh-positive, both recipient and donor to be Rh-negative, or the recipient to be too old to bear children.

This rule must be broken only if the patient is expected to die before Rh-compatible blood can be obtained.

We wish to acknowledge our debt to the staff of the department of obstetrics for much valuable help and advice, and for permission to review large numbers of their case records.

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As the result of negotiations between the Northern Ireland Ministry of Health and the Northern Ireland Pharmaceutical Negotiating Committee, the Committee has decided to recommend all chemists in Northern Ireland to enter the Health Service provisionally, pending the outcome of further negotiations. The Minister of Health (said an agreed joint statement) "undertook to appoint a practising accountant to carry out an investigation into dispensing costs in Northern Ireland and, after receiving the Accountant's report, to enter into further negotiations on the basis of this report and that made by the accountants appointed by the chemists, full account to be taken of pharmaceutical practice in Northern Ireland."

THE EVOLUTION OF GASTRIC AND DUODENAL ULCERATION

BY

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Acquired disease being the product of disharmony between constitutional and environmental factors, it is inevitable that alterations in mode of life should be accompanied by change in the pattern and distribution of certain diseases. As a preliminary to the present investigation the early literature dealing with peptic ulcer was reviewed and the observations thereon summarized in a previous communication (Craig, 1947). Space will not permit of further detailed discussion of the nature and incidence of peptic ulceration before the present century, but certain broad conclusions may be outlined.

Although gastric ulcer was mentioned by Celsus and was well recognized in the eighteenth century, the disease does not appear to have been at all common until the middle of the nineteenth century, when William Brinton (1857) concluded that about 5% of the population were subject to gastric ulcer at some time or other in their lives. At that time gastric ulcer was predominantly a disease of young women, many of whom suffered from perforation. Haematemesis occurred more commonly in men, generally in the fifth decade, but by the end of the century this complication, too, was one more often affecting young women (Hale White, 1901). Thus, although the overall incidence of gastric ulcer has remained fairly uniform during the past century, the age and sex distribution and its clinical pattern have changed very considerably in that time.

George Hamberger (1746) first described a case of duodenal ulcer, and Abercrombie (1828) gave the first account of the clinical features of the disease, but until the end of the century the amount of interest taken in the condition was out of all proportion to the number of cases encountered. The Fenwicks (1900), for example, were able to quote over 200 references, yet for all their extensive experience and keen interest they could gather together only 68 cases, 25 of them acute ulcers. It is generally believed that the apparent rarity of duodenal ulcer until the present century was the consequence of failure to recognize the condition. Undoubtedly many cases were missed, but when the situation is viewed against the broader background of earlier writings it is difficult to escape the conclusion that improvement in diagnosis was concomitant with an increase in the frequency of the disease. Review of more recent years provides strong evidence of further increase, and this suspicion becomes stronger. Although there is every reason to believe that duodenal ulcer has become very much more common there is no evidence that its clinical features have altered in any way.

Pringle (1753) and MacGregor (1804) in their treatises on military medicine made no mention of dyspepsia in the Army. In the war of 1914–18, digestive diseases of all types were no great problem, but in the recent war, by the end of 1941 no fewer than 23,754 serving personnel had to be invalided from the Army alone on account of peptic ulcer, duodenal ulcer preponderating over gastric ulcer in the ratio of approximately 7:2.

The changing nature and frequency of gastric and duodenal ulceration thus becomes apparent. The evolution of acute gastric ulcer, of chronic gastric ulcer, and of duodenal ulcer has been so different as to raise the strong suspicion that they may be distinct diseases, albeit related to one another. In an attempt to evaluate causal factors

it should not therefore be too readily assumed that gastric ulcer differs from duodenal ulcer only in its situation.

Statistics of the Registrar-General

Tidy, by analysis of the statistics of the Registrar-General for the years 1911–37, has shown that the increase in the crude death rate from peptic ulcer during this period is accounted for largely by the increase in deaths from gastric ulcer in men over 40. He has also pointed out the rapid diminution in the number of deaths from gastric ulcer in women under the age of 40. Jennings (1940), in a comprehensive historical survey of perforated peptic ulceration, has stressed the changing age and sex distribution of this condition, with particular reference to the period 1901–35.

In this present review death rates in the civil population have been analysed in selected years, up to and including 1945. The difficulties inherent in the interpretation of these figures are manifold, and in the past have perhaps been insufficiently stressed. Acceptance of these statistics as accurate implies an assumption that the great majority of death certificates correctly assign the cause of death, and this is a bold surmise when dealing with two diseases—gastric and duodenal ulceration—which are so readily confused with one another and the latter of which was widely recognized only recently. Secondly, such statistics refer to only a small proportion of ulcer sufferers—some 5% or so—who die from the direct effects of their ulcers. Finally, in trying to assess disease trends, it is almost impossible to evaluate the effect of therapeutic changes.

From the year 1940 a change was made in the manner of selecting the assigned cause of death where more than one cause was mentioned in the death certificate, the choice then being "that in the main inferred from the statement of the certifier instead of being determined by arbitrary rules of precedence." This change had the effect of producing an apparent increase of about 4% in the mortality rate of peptic ulcer. If the crude death rate for all forms of peptic ulcer be plotted graphically for the years 1910–45 it will be noted that no very significant fluctuation occurred between the years 1911 and 1921, after which there was a very sharp and uninterrupted rise till 1927. From then until 1939 this rise was less marked and was interrupted by minor falls; but the year 1940 saw the sharpest rise hitherto recorded, the rate remaining at the same high level in 1941, falling back to its original level in 1942, and then rising steadily and fairly steeply till the year 1945. Only about one-fifth of the increase in 1940 could be accounted for by the new method of selecting the cause of death.

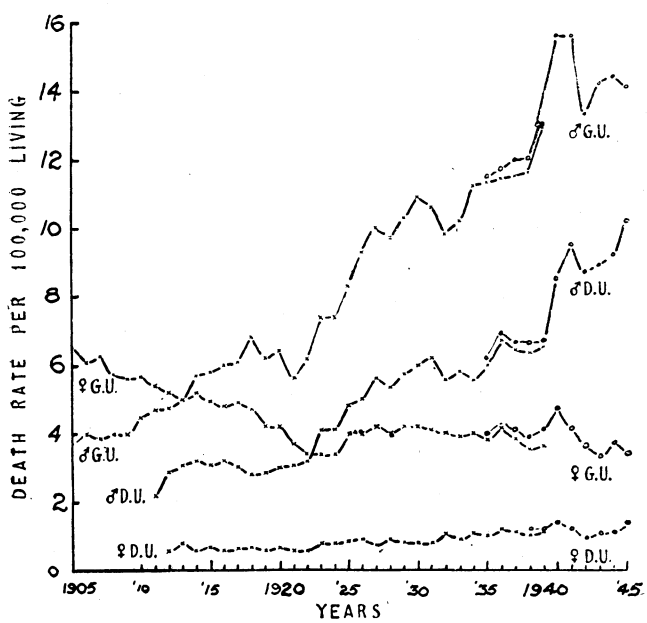

FIG. 1.—Crude death rates per 100,000 living for gastric ulcer and duodenal ulcer from 1905 to 1945. During the periods of the two world wars non-civilian figures are excluded. For the years 1935–9 inclusive the graphs show rates (*a*) based on the revised method of assignment (o-o-o) and (*b*) based on the old method of assignment (x-x-x).

In Fig. 1 the death rates from gastric ulcer and duodenal ulcer are plotted separately for the two sexes. From 1940 onwards the figures are based on the new method of assessment : before 1935 they are based on the old method. For the years 1935–9 inclusive two sets of figures are plotted—those based on the old method and those based on the new method. It will be seen that the change in the method of assigning the cause of death makes no significant alteration to the general trend. The increased mortality rate is accounted for largely by the increased death rate from gastric ulcer in males and to a smaller extent from duodenal ulcer in males. Although duodenal ulcer in females has been a steadily increasing cause of death the mortality rate from gastric ulcer in women has fallen fairly steadily and uninterruptedly, with the exception of the year 1940, when there was a significant rise in the death rate from both forms of ulcer in both sexes. At all times, in both sexes, gastric ulcer has been a commoner assigned cause of death than has duodenal ulcer.

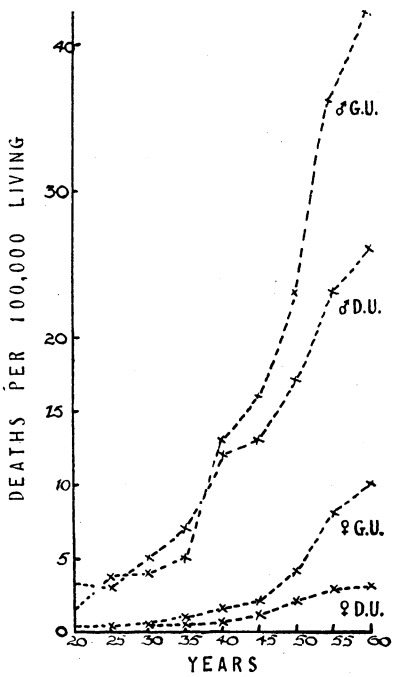

FIG. 2.—Civilian death rates per 100,000 living from gastric and duodenal ulcers in both sexes at various ages, for the year 1945. In male Service personnel at all ages in this year the corresponding rates were: D.U. 1.2, G.U. 1.5, per 100,000 living.

Population Trends

It is pertinent to determine how far these fluctuations in crude mortality rates represent a response to alterations in the age distribution of the population. It is common experience that the mortality from perforation, haemorrhage, and operation increases with age. Analysis of the figures for the year 1945 shows that the death rate from all forms of ulcer increased steadily with age (Fig. 2). By plotting graphically the proportion of the population (*a*) over the age of 45, and (*b*) over 65, one can demonstrate that these older sections of the community are increasing steadily. Similarly, it may be shown that an increasing proportion of ulcer deaths occur in these two older groups, and in the following table the population distribution during the years 1911 and 1942 is compared.

	1911	1942
Proportion of population over 45	21%	35%
,, ,, all peptic ulcer deaths over 45 ..	37%	90%
Proportion of population over 65	5%	10%
,, ,, all peptic ulcer deaths over 65 ..	10%	31%

It is therefore apparent that the increase in the death rate in the older groups is out of proportion to their greater numbers and that the brunt of the overall increased death rate is being borne by these older people ; but these figures alone give no indication of changing death rates in the other sections of the community.

Accordingly, death rates for gastric ulcer and for duodenal ulcer per 100,000 living were plotted in various age and sex groups for selected years from 1911 to 1945, inclusive. Limitations of space will not permit publication of all these graphs, but their trends will be briefly summarized.

General.—In both sexes and all age groups gastric ulcer has proved a more common assigned cause of death than has duodenal ulcer, despite the fact that in all carefully investigated modern series duodenal ulcer is much commoner than ulcer in the stomach. This may argue a higher mortality rate from gastric than from duodenal ulcer, but it may be only a reflection of the tendency of many practitioners to refer generically to a "gastric ulcer" whether the lesion be in the stomach or the duodenum. None the less, the view that gastric ulcer is more commonly fatal than duodenal ulcer is in accord with the military figures for 1940–2 and gastric ulcer deaths in the Services during the year 1945 again preponderated over duodenal ulcer deaths in the proportion of 5 to 4. These rates are lower than those in the corresponding civilian group owing to the medical selection before enlistment and the early invaliding of sufferers.

Death Rates in Males Under 45.—These curves show the fluctuations which inevitably occur when fairly small numbers are being considered. Although the death rate from both gastric and duodenal ulcer did not vary greatly between the years 1915 and 1939, it is perhaps significant that the therapeutic advances made during this period did not result in any appreciable lowering in mortality in this group. No weight can be attached to the rise during the war years, for these figures refer only to the civilian population, which then contained an abnormally high proportion of unfit men rejected for military service.

Death Rates in Older Men.—Some of these are charted in Fig. 3, which demonstrates the increasing incidence over the period reviewed, the increasing mortality with age, and the greater mortality from gastric ulcer than from duodenal ulcer.

Death Rates in Women.—The outstanding feature of these curves is the remarkable fall in gastric ulcer mortality in all except the very oldest (Fig. 4). The death rate from duodenal ulcer has always been small, and it has remained fairly constant in particular age groups, the overall increase in such mortality (Fig. 1) resulting very largely from the ageing nature of the population.

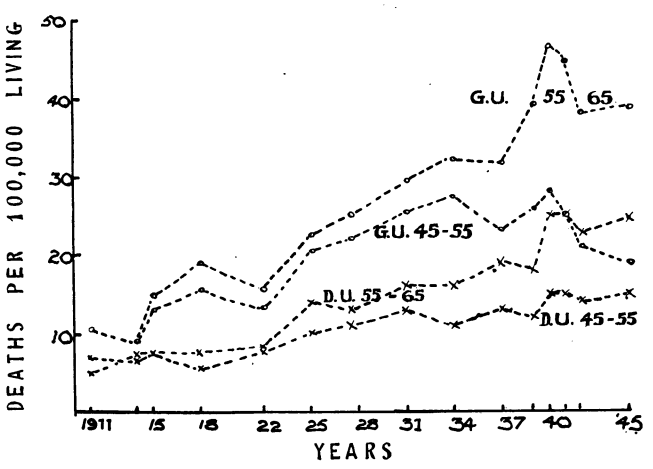

FIG. 3.—Male death rates per 100,000 living from gastric and duodenal ulcer in selected years from 1911 to 1945, in the age groups 45–55, 55–65; non-civilian males are excluded in the years of the two World Wars.

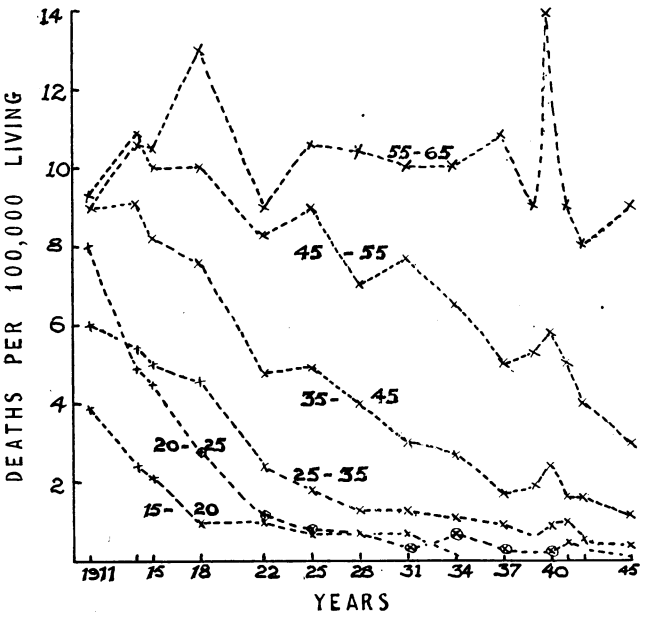

FIG. 4.—Female death rates per 100,000 living from gastric ulcer in various age groups for selected years from 1911 to 1945, non-civilian females being excluded in 1942 and 1945.

The Changing Incidence of Perforation

Although in the year 1945 the mortality from both duodenal and gastric ulceration in both sexes increased with age, corresponding analysis of deaths for the year 1911 (Fig. 5) showed a high peak of mortality from gastric ulcer in young women. The lowering of the death rate in these young women is the result of the virtual disappearance of gastric perforation in this group. In 1907 Hawkins and Nitch, reviewing 556 cases of gastric ulcer treated at St. Thomas's Hospital, gave details of 92 cases of perforation, only 30 of which occurred in men. In this series perforation in men occurred most often over the age of 40 ; in women the great majority of cases occurred between the ages of 15 and 25. The curve obtained by plotting these cases in age groups is substantially the same as that derived from charting the details of Brinton's (1857) cases of 199 perforations, only 60 of which occurred in men. From the details accompanying this communication of Hawkins and Nitch it appears that at least half of the ulcers which perforated in young women were chronic in character, the perforations being preceded by a long history of dyspepsia and the ulcer bed being scarred. This age-and-sex incidence of peptic perforation is in striking contrast to the experience of Illingworth, Scott, and Jamieson (1946), who reviewed 880 cases of perforation occurring between 1938 and 1943, 95% of them in men, the perforation being in the duodenum in 87% of cases. In their series the commonest age at perforation was between 35 and 50.

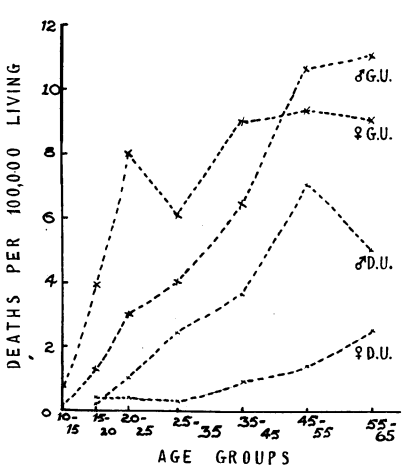

FIG. 5.—Death rates per 100,000 living from gastric ulcer and duodenal ulcer in various age groups for the year 1911.

These findings tally closely with figures collected by Boggon, by Forty (1946), and in a series at St. Mary's Hospital over the past ten years. That Illingworth's series consisted almost entirely of chronic ulcers is indicated by the fact that in the absence of medical treatment a great majority of cases relapsed within five years, some 20% of them suffering further major complications.

All earlier works consulted agree on the age-and-sex incidence of gastric perforation, but the only series of perforated duodenal ulcer found after prolonged search is the small one collected from the literature by Moynihan and published by him in 1905. The relative rarity in females is apparent, and it seems that on the whole these perforations occurred at an earlier age than those in the series of Illingworth *et al.* The difference, however, is not sufficient to be significant.

Apart from the evidences of the changing nature of gastric ulcer in women, the most striking features of these analyses are:

1. The striking proof of the ageing nature of our population.

2. The evidence of increased mortality in the older age groups.

3. The steady rise in total peptic ulcer deaths between the years 1921 and 1939, with a well-marked sudden increase in 1940 and 1941, this increase affecting the mortality from both gastric and duodenal ulcer in both sexes and all age groups. It has been pointed out by Illingworth that there was a marked increase in the incidence of perforation in the autumn of 1940 and the spring of 1941—that is, at the time when the real seriousness of the late war was first brought home by the defeat of the French armies and the bombing of this country. As Illingworth has further pointed out, this prevalence of perforation was not confined to areas subject to aerial bombardment. It is, however, legitimate to infer that the nervous strain and anxiety engendered by circumstances was nation-wide. The 1942 fall in death rate is the most pronounced during the period of observation. The explanation is perhaps that the circumstances which produced the rise in 1940 and 1941 advanced the death of some who might otherwise have survived till 1942 or 1943, and the population during these latter years therefore contained relatively fewer of the less hardy elements.

4. The maintenance or actual increase in death rate from duodenal ulceration in all age groups despite therapeutic advances, particularly in the treatment of perforation and haemorrhage—a circumstance which suggests that the actual incidence of the disease in the population at large has undergone a considerable increase.

5. Only in gastric ulceration in young women has there been any striking decrease in mortality. This has been the result not of corresponding increase in medical knowledge but of some unknown evolutionary process. It is perhaps significant that chlorosis, once a frequently associated disease, has now virtually disappeared.

Conclusions

Certain difficulties inevitably arise in the course of any attempt to trace the history of a disease. Earlier accounts are based on very imperfect knowledge, the growth of understanding having paralleled the evolution of the disease. Yet certain writings stand out, and one feels that the observations contained therein are reliable even though it may be difficult to communicate this confidence to others. The inadequacies of death-rate statistics has already been stressed, but a review of these figures affords an idea of the trend which a disease is taking. Military surveys and series of cases of perforation published at different periods strongly suggest that the pattern and distribution of gastro-duodenal ulceration have materially changed. When all the evidence from these independent sources is entirely consistent certain conclusions may be drawn.

It would appear that gastric ulceration, at least in its present form and prevalence, is a disease of comparatively recent evolution, and there is good reason to believe that ulceration of the duodenum is a disease of even later development.

While, so far as can be ascertained, duodenal ulceration has simply increased in frequency during the period under survey, it is clear that in the case of gastric ulcer not only the age and sex distribution but even the actual nature and clinical pattern have altered considerably during the last hundred years or so, although it is probable that the total incidence has not undergone any very striking increase. In the time of William Brinton gastric ulcer principally affected women, and the ulcer seems to have been very similar to that which we encounter to-day, although a small proportion of chlorotic young women developed perforation of an acute ulcer. Haematemesis in young women was relatively uncommon, most women so affected being in their fifth decade. At the beginning of the present century chronic gastric ulcer was becoming relatively more frequent in males, but a larger number of women of child-bearing age suffered from haematemesis due to acute superficial ulceration. Gastric perforation was predominantly a disease of young women. It is difficult to determine exactly when this state of affairs altered, but it is probable that the change occurred during the period of the first world war.

In the course of the preceding investigation the changes in the incidence, distribution, and pattern of the various forms of peptic ulceration have been traced in some detail. It will be seen that these changes are complex, and that if we are to accept the proposition that peptic ulcer is one single clinical entity, the result of the operation of one set of aetiological factors, then it is difficult if not impossible to see how these changes could have taken place. On this historical evidence alone, even if on no other, a clear-cut distinction may be made between gastric ulcer and duodenal ulcer as separate diseases with different mortality trends. A similar distinction must be made between the chronic type of ulcer, whether sited in the stomach or the duodenum, and the acute variety. In the past the many features which these conditions possess in common have tended to obscure their essential differences and therefore led to some confusion of thought in the study of their causation. It cannot be gainsaid that all these diseases are probably related to one another, but that is not to say that they are different manifestations of the same disease process. It is suggested that such confusion and difficulty will inevitably arise in the study of these diseases unless they be considered individually until further knowledge permits of evaluation of the features they have in common. For the present it must be stressed that the history and evolution of gastric ulceration in its various forms are so very different from those of duodenal ulceration as to stamp the two conditions as separate entities.

While it cannot be denied that constitutional factors may play an important part in the pathogenesis of peptic ulceration in its various forms, it is difficult to believe that fluctuations in such factors alone could be responsible for the many changes which have occurred, and these must therefore be attributed to changing environmental influences. In view of the convincing evidence of gross increase in the prevalence of gastric and duodenal ulceration the view that they are concomitants of life under modern conditions is to a large extent substantiated.

Summary

Alterations in the incidence, age-and-sex distribution, and clinical features of gastric and duodenal ulcer are surveyed over a period of years.

In particular the changes which have occurred during the present century are examined on the basis of clinical surveys, the Registrar-General's returns, and post-mortem statistics.

It seems probable that gastric ulceration was uncommon until the beginning of the nineteenth century, and there is little evidence to suggest that duodenal ulceration was other than a rare disease until about the beginning of the present century.

Since that time there is evidence of a considerable increase in the incidence of duodenal and gastric ulcer in males. Although gastric ulcer in females has become very much rarer, investigations point to an increase in the frequency of duodenal ulcer.

The increased mortality from gastric and duodenal ulcer in males and from duodenal ulcer in females affects principally those in the later age groups, and the ageing nature of the population therefore results in an increase in total mortality which is thus more apparent than real. But even in the younger age groups mortality has either risen or remained steady, except that the mortality from gastric ulcer in young females has shrunk to negligible proportions.

Peptic ulceration is a disease which causes considerable morbidity in relation to its mortality rate. The mortality from gastric ulcer apparently exceeds that from duodenal ulcer quite apart from any deaths which may result from neoplastic change in a gastric ulcer.

Although little change can be detected in the nature of duodenal ulceration it is clear that the pattern of gastric ulceration has altered profoundly during the last 100 years.

The various forms of peptic ulceration, gastric and duodenal, acute and chronic, can from the aetiological point of view be regarded as quite separate, although they are almost certainly related conditions.

The cause of these changes, and accordingly the causation of the diseases themselves, are to be sought in environmental circumstances rather than in constitutional factors.

There is considerable support for the view that the evolution of gastric and, more particularly, duodenal ulceration has paralleled the development of the highly developed civilized state of to-day.

I am indebted to Dr. J. F. Ackroyd, Dr. T. C. Hunt, and Professor G. W. Pickering for invaluable criticism and advice in the preparation of this paper.

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SOME PROBLEMS OF CAUSALGIC PAIN

A CLINICAL AND EXPERIMENTAL STUDY*

BY

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Ever since Weir Mitchell and his colleagues at the time of the American Civil War drew attention to the occasional occurrence of persistent pain and tenderness following nerve injuries and amputations (Mitchell, Morehouse, and Keen, 1864; Mitchell, 1872) these conditions have presented many intriguing problems. There have, however, during recent years been some advances in our knowledge of these distressing cases.

Lewis (1937) found that in some subjects cutaneous tenderness could be produced through nervous channels—for example, by stimulating a cutaneous nerve with a weak faradic current. As a result of his investigations he concluded that such hyperalgesia was due to nerve impulses leading to the liberation of a pain-producing chemical substance from cellular elements in the skin, and that the nerves concerned were not sympathetic nerves or ordinary sensory nerves, but special nerves belonging to the posterior root system. These nerves he named nocifensor nerves, and the hyperalgesia they produced nocifensor hyperalgesia. It seemed to Lewis, and has seemed to many others since, that this experimental hyperalgesia must in some way be related to hyperalgesia following nerve injuries, though apparently at variance were Lewis's finding that experimental nocifensor hyperalgesia could be produced after the degeneration of sympathetic nerves to the skin following sympathetic ganglionectomy and the relief of causalgic pain and hyperalgesia that is often achieved by sympathectomy.

Homans (1940), among others, has drawn attention to cases of nerve injuries in which hyperalgesia develops without spontaneous pain or at least without burning pain. He suggested that the difference between these cases and cases of classical causalgia with burning pain was only one of degree, and to describe them he used the term "minor

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