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METABOLIC EFFECTS OF PARTIAL GASTRECTOMY

WITH SPECIAL REFERENCE TO CALCIUM,

FOLIC ACID AND VITAMIN B₁₂

THESIS

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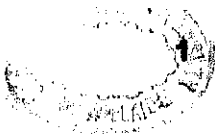
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The aetiology of peptic ulceration remains unknown, and so it is not surprising that medical treatment is unsatisfactory. Of the measures currently employed in the medical management of ulcers, a significant increase in the likelihood of healing has been demonstrated only for bed rest in hospital (Doll and Pygott, 1952), the discontinuance of tobacco smoking (Doll, Jones and Pygott, 1958) and the administration of stilboestrol (Truelove, 1960). Indeed, there is no proof that medical treatment has any favourable influence on the life history of the disease. At the present time patients with intractable and life-threatening peptic ulceration are frequently treated surgically. Avery Jones (1957) has estimated that about one-half of the patients with gastric ulcer and one-third of those with duodenal ulcer need surgical relief. The benefits of gastric surgery are the removal of the threat to life from the ulcer, and the relief of ulcer symptoms. Permanent relief of ulceration, freedom from serious side effects and the ability to work and enjoy life are claimed to be achieved in 90 per cent. of cases (Pulvertaft, 1952; Brookes, Waterhouse and Thorn, 1960). Operative deaths and recurrent ulceration account for less than 5 per cent. of failures, and other serious effects of gastrectomy for the rest. Many of the 90 per cent. of "successes" however, are acknowledged to suffer from minor symptoms or are found to be nutritionally subnormal.

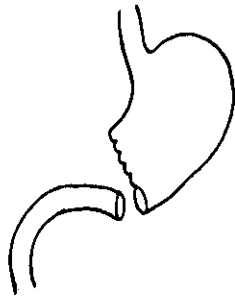
In recent years it has been recognised that ill-health following gastric resection is more serious than previously acknowledged, and that the consequences of such operations may lead to new disease processes

(Illingworth, 1960; Welbourn, 1960; Welch and Ellis, 1961). It has been found that procedures which eliminate the ulcer satisfactorily are often followed by undesirable after effects.

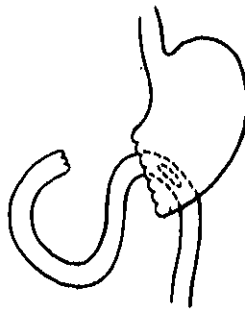
The dilemma of gastric surgery which accounts for the striking vogues and fashions in operative procedure (Fig. 1) is that a limited resection may lead to recurrence of the ulcer, whereas a more extensive operation is liable to be followed by troublesome symptoms resulting from the loss of the reservoir function of the stomach.

Difficulties encountered after operation are recurrent ulceration; the early post-prandial or "dumping" syndrome; bilious vomiting; the late post-prandial or hypoglycaemic syndrome; and disturbances of nutrition (Illingworth, 1960). Foremost amongst the abnormal nutritional states are loss of weight (Zollinger and Ellison, 1954) and iron deficiency anaemia (Morley and Roberts, 1928; Gordon-Taylor, Hudson, Dodds, Warner and Whitby, 1929). Less commonly detected are megaloblastic anaemia (Badenoch, Evans, Richards and Witts, 1955); steatorrhoea (Wollaeger, Comfort, Weir and Osterberg, 1946); osteomalacia (Pyrah and Smith, 1956); hypoproteinaemic oedema, beri-beri and Wernicke's encephalopathy (Welbourn, 1960); and subacute combined degeneration of the spinal cord (Bastrup-Madsen, 1954). The problem of ill-health after operation is of considerable magnitude as there may well be 20,000 patients in Australia alone who have had gastrectomies.

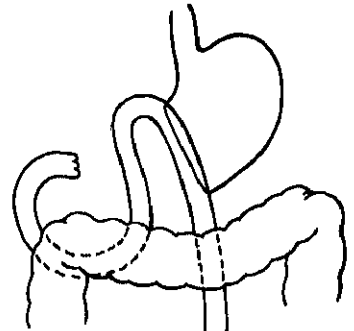
Operations on the stomach are designed to produce certain alterations in the physiology of the stomach. Reduction in the secretion of hydro-



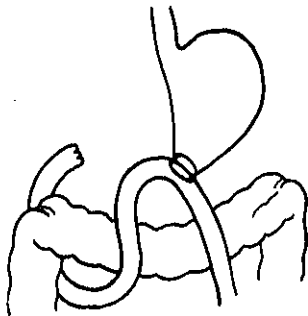
BILLROTH I
1881



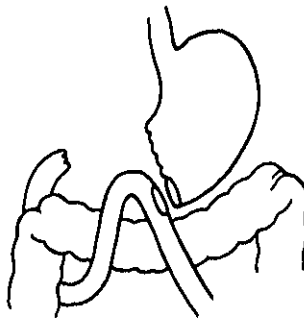
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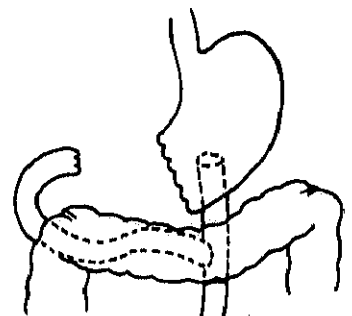
POLYA 1911



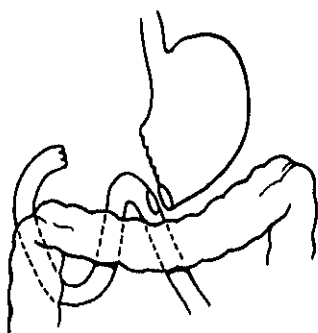
KRONLEIN. 1888



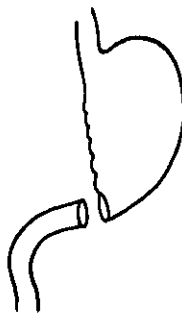
v. EISELSBERG. 1889



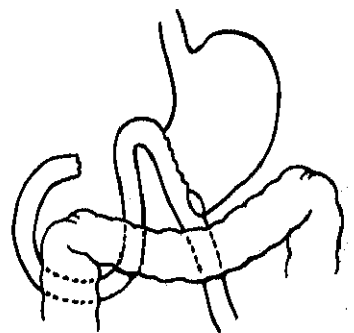
ROUX. 1893



HOFMEISTER. 1908



SCHOEMAKER.
1911



FINISTERER. 1914.

Figure 1: Methods of restoring gastro-intestinal continuity in the operation of partial gastrectomy. The term Billroth I is commonly used for partial gastrectomy with gastro-duodenal anastomosis, and the term Polya for partial gastrectomy with gastro-jejunal anastomosis.

chloric acid and pepsin is a major objective in the surgery of peptic ulceration. Unfortunately the physiological consequences of operation are not restricted solely to these. Indeed gastrectomy provides the investigator with an experimental situation in which the importance of the stomach with respect to many physiological processes can be usefully studied. After operation there can be impaired absorption of carbohydrates (Gryboski, Thayer, Gryboski, Gabrielson and Spiro, 1963); fats (Wollaeger et alii, 1946); proteins (Crane, 1961); vitamin A (Althausen, Uyeyama and Loran, 1960); vitamin B₁ (Markkanen, 1960); vitamin B₁₂ (Badenoch et alii, 1955; Baird and Wilson, 1959); potassium (Sensenig and Campbell, 1957); and calcium (Nicolaysen and Ragård, 1955a). However, it should be recognised that despite this formidable number of changes, the capacity of the body to adjust satisfactorily is such that in the majority of subjects post-operative sequelae are relatively unimportant when compared to the subjective relief obtained by the patient.

It should be noted at this stage that there is a marked variability in the reported incidence of the frequency and severity of post-operative symptoms. The incidence of conditions such as anaemia, and the "dumping" syndrome varies from unit to unit and it is most probable that those who report a low incidence have included only patients who complain spontaneously. Close questioning and detailed examination including relevant laboratory studies will uncover a higher percentage of unsatisfactory results. Some patients refrain from mentioning post-

operative symptoms to the surgeon who performed the operation through fear of causing displeasure or appearing ungrateful. They will nevertheless unburden their troubles to an independent third person.

Furthermore many symptoms after operation - weakness, fatigue, palpitations, flushing, drowsiness and anorexia - are complained of by many neurotic subjects as well. It is therefore easy to dismiss the patient's illness as neurosis, especially when it responds poorly to treatment.

However the degree of disability that post-gastrectomy symptoms cause varies enormously and cannot always be explained by differences in the type of anastomosis, size of the stoma, length of the afferent loop and other technical factors. The patient's pre-operative personality and his attitude to the operation and subsequent discomfort are of cardinal importance. Symptoms are more common and more severe in apprehensive, maladjusted, idle or otherwise insecure people. They are more common if a patient with only mild ulcer symptoms is operated on and for these patients sometimes, the cure appears worse than the original disease. The patient who has had many years of suffering before operation, on the other hand, judges the severity of his post-gastrectomy symptoms with his past discomfort. He is frequently pleased with the results of surgery. These considerations have led to the suggestion that patients should be made to "earn" their gastrectomies, by enduring their ulcer symptoms for a sufficient period of time so that any discomfort following operation is bearable by comparison. This attitude

of "trial by ordeal" further serves to underline the fact that undesirable effects not infrequently follow operation.

Another factor accounting for the variability in the reported frequency of post-operative sequelae is the likelihood that the frequency will depend on the degree and thoroughness with which they are searched for. Furthermore the precision of diagnosis, especially in the various metabolic disturbances, will be influenced by the level of sophistication of the laboratory techniques that are available for use.

The clinical investigator, particularly if he is not a surgeon, runs the risk of over-estimating the severity of post-gastrectomy disabilities and of under-estimating the benefit of the operation to the patient. To minimize this bias, it is important that the investigator establishes a causal relationship between the patient's symptoms and the operation. Furthermore the frequency of a symptom or syndrome following gastrectomy should be compared with the frequency in a comparable sample of the population which has not had the operation. It is also desirable that the assessment be made on objective data and not limited simply to the analysis of subjective impressions. Lastly, in circumstances where observer bias could significantly influence the results, the assessment should be made by one observer who is kept unaware as to the particular category, gastrectomy or control, to which each patient belongs. An approach along these lines has been attempted in the studies reported in this thesis.

The investigations on which this thesis is based represent a

continued interest in the problems of post-gastrectomy patients which began five years ago with a study of the anaemias after operation. A review of the haematological data from 33 gastrectomy follow-up investigations comprising 7,505 patients made at that time, showed that although anaemia was present in 28 per cent. it was megaloblastic in only 0.33 per cent. The frequency of megaloblastic anaemia in these reports is not appreciably higher than would be expected in a population of similar genetic constitution which had not been operated on (Diascombe, 1960) and is in accord with the prevailing assumption that the association of the anaemia and operation is coincidental (Jones and Gummer, 1960). In the previous studies undertaken by me it was shown that megaloblastic anaemia was considerably more frequent after gastrectomy than the literature had hithertofore suggested. Of 265 patients who had had partial gastrectomy one to twelve years previously for peptic ulceration, megaloblastic anaemia was found in 1.5 per cent. of patients, transitional megaloblastic anaemia in 5.3 per cent. of patients, and a level of vitamin B₁₂ in the serum below the normal range in 14 per cent. of patients (Deller and Witts, 1962). The fall in the serum level of vitamin B₁₂ commenced one year after operation and progressively fell for six years. Anaemia was present in 20 per cent. of both males and females and a significant correlation was observed between serum iron levels and anaemia. Two-thirds of the anaemias were of the iron deficiency type and the remainder either dimorphic or due to vitamin B₁₂ deficiency alone. The marrow was at least partially megaloblastic

in almost half of those examined.

Further evidence was provided in these studies to indicate that the association of megaloblastic anaemia and operation was not fortuitous (Deller, 1962; Deller, Richards and Witts, 1962). Patients with megaloblastic changes after operation had free gastric hydrochloric acid before operation and the histology of the resected stomachs was unlike that in pernicious anaemia. At the time of investigation the majority of patients had low serum levels of iron and vitamin B₁₂, impaired absorption of radioactive vitamin B₁₂ corrected by intrinsic factor administration, steatorrhoea, achlorhydria, reduced uropepsinogen excretion, atrophic gastritis and jejunitis. The cause of the anaemia was considered to be deficiency of vitamin B₁₂ resulting from reduced secretion of gastric intrinsic factor. Intrinsic factor deficiency followed resection of part of the stomach which secretes intrinsic factor and progressive atrophy of the remaining mucosa (Figure 2).

In this thesis the study of post-gastrectomy anaemia has been extended, and in addition a study has been made of another aspect of disturbed metabolism after operation. The role of folic acid deficiency in the pathogenesis of anaemia following operation was studied because this has not been investigated previously in any detail. The second haematological study consists of an investigation into factors influencing the absorption of radioactive vitamin B₁₂ after partial gastrectomy. Evidence has been presented to show that the impaired absorption is due to a deficiency in intrinsic factor and possibilities other than this, for

example, the presence of an abnormal bacterial flora, the development of jejuno-ileal insufficiency, and the unavailability of calcium in steatorrhoea, are examined in the present study. Lastly a comprehensive investigation has been made into disturbances of calcium metabolism and the bones after partial gastrectomy.