BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 30 1960

SOME SURGICAL ASPECTS OF THE MALABSORPTION SYNDROME*

BY

ANDREW W. KAY, M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S.
Professor of Surgery, University of Sheffield

The nutritional status of man depends on an adequate intake of food followed by its efficient digestion and absorption from the intestine. While numerous factors within the intestinal lumen, such as pH, motility, mucosal surface, bacteria, secretory hormones, and certain disease states, are known to influence absorption from the intestine, the precise processes whereby the nutritional products of digestion are absorbed into the blood-stream to be transported to the metabolic pools of the body remain obscure.

The malabsorption syndrome presents a challenge to those concerned in its treatment, and poses many problems which have stimulated research in many different fields. Thus the physiologist is attracted by the evidence of abnormal gastro-intestinal function; the haematologist by changes in absorption of vitamin B₁₂, folic acid, and iron; the nutritionist by the discovery that dietary factors may play a part in aetiology; the biochemist by the possibility of alterations in the metabolism of calcium, potassium, and lipids; and the bacteriologist by the unresolved enigma of the intestinal flora. For these reasons the malabsorption syndrome provides a common meeting-ground for workers in a number of different disciplines. The surgeon has an important part to play in this co-operative research. By his manipulations and resections of the small intestine he may inadvertently produce the syndrome; by further surgery he can sometimes effect its cure; by virtue of his scientific training—and this can be his greatest contribution—he has a unique opportunity to glean vital information from these surgical experiments.

Of the many aspects of the malabsorption state which interest surgeons, I have elected to consider some causes directly attributable to operative alteration of the continuity, motility, or digestive secretions of the gastro-intestinal tract. Malabsorption due to gastrectomy, vagotomy, "culs-de-sac," gastro-colic fistula, and massive resection of the small intestine is discussed with special reference to the mechanisms responsible for gastro-intestinal dysfunction.

Malabsorption after Gastrectomy

Impaired nutrition after gastrectomy is commonly the result of reduced intake of food. In some patients, however, malabsorption plays an important part, and may lead to severe loss of weight, steatorrhoea, and even vitamin deficiencies (Anderson *et al.*, 1955).

Reduced intake is an important cause of impaired nutrition after gastrectomy in patients who are aware

of a feeling of fullness and discomfort after meals and who consequently tend to limit the size of their meals. It would seem a simple matter to encourage such patients to increase their intake of food, but, unfortunately, when the loss of food in the faeces is greatest the capacity for food is often smallest. The best advice for this group of patients is to encourage them to take frequent small meals. In severe cases, jejunal or colonic replacement procedures, by providing a food reservoir, are rational and are worthy of consideration.

Impaired absorption of food after gastrectomy may be due to any one or to any combination of the following factors.

Possible Causes of Post-gastrectomy Malabsorption

1. Rapid gastric emptying and intestinal passage of food.
2. Impaired pancreatic-biliary digestion from:
 - (a) Inadequate mixing of food with secretions.
 - (b) Inadequate production of secretions.
3. Activation of latent steatorrhoea.
4. Afferent loop (Polya) acting as cul-de-sac.
5. Bacterial colonization of jejunum.

Rapid gastric emptying and intestinal passage of food, more pronounced after Polya than after Billroth I gastrectomy (Meurling, 1953), predispose to malabsorption by reducing the contact time between intestinal contents and absorbing surface. The more normal pattern of emptying from the stomach and upper intestine in Billroth I patients has been neatly confirmed by adding radio-iodinated human serum albumin to a test meal and employing the technique of "external counting" (Lundh, 1957). After total gastrectomy there is an extremely rapid intestinal passage of the meal.

The hormones secretin and pancreozymin, liberated into the blood-stream by the action of gastric hydrochloric acid on the duodenal mucosa, stimulate the secretion of pancreatic juice and provoke contraction of the gall-bladder. These mechanisms, essential for normal digestion, may be deranged in one of the following ways after gastrectomy.

Firstly, in Polya gastrectomy (gastro-jejunal anastomosis) food precedes the bile and pancreatic secretions down the small intestine, instead of meeting and merging with it. It is not surprising, therefore, that the faecal excretion of fat is usually greater after Polya than after Billroth I gastrectomy—gastro-duodenal anastomosis (Wollaeger, 1950). When this factor is judged to be of major importance in the production of steatorrhoea a conversion operation (Polya to Billroth I) is indicated. Secondly, the secretin and pancreozymin mechanisms are inactivated in patients who fail to secrete acid after gastrectomy, and malabsorption may follow. Attempts to remedy this defect by the administration of dilute hydrochloric acid or by pancreatic enzyme

*Read to the Section of Surgery at the Joint Annual Meeting of the British Medical Association and Canadian Medical Association, Edinburgh, 1959.

substitution therapy have yielded very variable results; some of the failures may be explained on the basis of inadequate dosage. Finally, while many patients continue to secrete appreciable amounts of acid after partial gastrectomy, this stimulus for the release of secretin and pancreozymin can be effective only after gastro-duodenal anastomosis; a gastro-jejunal anastomosis permits the acid to escape directly into the jejunum. A conversion from Polya to Billroth I may be beneficial in selected cases.

Paulley and his colleagues (1957) postulate that severe steatorrhoea and loss of weight after gastrectomy may be due to aggravation of a latent idiopathic steatorrhoea. They have gained support for this hypothesis by showing a correlation between the state of the jejunal mucosa (biopsied at the time of gastrectomy) and the patient's subsequent progress, and conclude that jejunal biopsy may prove a useful screening measure before gastrectomy.

It has been suggested that the afferent loop of a Polya gastrectomy may cause malabsorption by acting as a cul-de-sac. However, this particular loop of intestine is exceedingly active, empties itself readily (regularly observed on screening after a barium meal), and is normally washed through by bile and pancreatic juice after each meal. Thus it does not permit the stagnation of intestinal content which is critical for the development of a "cul-de-sac" syndrome (see below).

Finally, it has been suggested that the vitamin-B deficiencies which occasionally follow gastrectomy are due to colonization of the jejunum by organisms from the lower bowel which compete with the host for the vitamins (Welbourn *et al.*, 1951). However, while *Cl. welchii* are often present in large numbers in the contents of the gastric remnant during the first week after gastrectomy, a study of specimens of jejunal content from post-gastrectomy patients with loss of weight and anaemia showed no evidence of continued colonization of the upper small intestine (Duncan *et al.*, 1954).

Malabsorption after Vagotomy

Vagotomy as a sole therapeutic procedure is followed by troublesome symptoms (distension, foul eructations, nausea, vomiting, and diarrhoea) which are largely preventable by the addition of a drainage operation such as gastro-jejunostomy or pyloroplasty. Diarrhoea after either of these procedures (emphasized as a frequent and serious disadvantage by surgeons who prefer gastrectomy) is not, in my experience, a common or troublesome complication. In a follow-up study of 661 consecutive vagotomy and gastro-enterostomy operations, Feggetter (1959) found 28 patients who complained of diarrhoea, an incidence of 4.3%. In most cases the alteration in bowel habit is a welcome correction of the constipation commonly associated with ulcer dyspepsia; in some there may be a history of several loose stools in the morning; in a few the diarrhoea is associated with intestinal malabsorption. In this last group the impaired absorption of food may be due to one or more factors.

Though the secretin and pancreozymin mechanisms are unlikely to be disturbed greatly by the drop in gastric acid secretion which follows vagotomy, these may be nullified when the available acid by-passes the duodenum through a gastro-jejunostomy; this is a reason for preferring pyloroplasty to gastro-jejunostomy as the drainage procedure.

On the basis that the diarrhoea is due to loss of the nervous component of pancreatic secretion consequent on division of the pancreatic branches of the vagus, Burge and Clark (1959) have developed the operation of selective vagotomy with preservation of the coeliac division of the posterior nerve. This ingenious operation merits controlled comparison with standard vagotomy in relation to the incidence of diarrhoea and of recurrent peptic ulceration. The aim of vagal section in the treatment of duodenal ulcer is to reduce the secretion of hydrochloric acid, and selective vagotomy will not supplant complete vagotomy unless it can be shown to be equally effective in this respect.

Post-vagotomy diarrhoea has been attributed by some to stasis and by others to intestinal hyperactivity (Fox and Grimson, 1950). Apparently irreconcilable, either may predominate in the individual case. It is difficult to predict the net effect upon motility of interrupting the vagal pathways, and familiarity with this procedure has taught us that the function of the extrinsic nerves is not to supply the gut with motor power from without but rather to adapt the motility inherent in the bowel to conditions and needs in other parts of the organism.

"Cul-de-sac" Syndrome

That ulcerating lesions of the small intestine may bleed and give rise to microcytic anaemia has been fully appreciated by surgeons for many years. Renewed interest in the small bowel has followed the demonstration that macrocytic anaemia and steatorrhoea may occasionally follow operations which result in the formation of by-passed loops or culs-de-sac in which intestinal contents can stagnate (Watson and Witts, 1952). This symptom-complex has also been reported in a number of diverse intestinal abnormalities, including intestinal stricture and massive diverticulosis. The cul-de-sac syndrome involves two groups of symptoms: firstly, intestinal dysfunction results in malnutrition, steatorrhoea, macrocytic anaemia, and vitamin deficiencies; and, secondly, the anatomical abnormality may cause symptoms of recurring intestinal obstruction.

The malabsorption is probably the result of an altered bacterial flora in the intestine which is apt to occur only when the arrangement of the cul-de-sac permits stagnation of its contents. Thus Cameron *et al.* (1949) found that blind loops fashioned to ensure ready emptying had no effect on the nutrition of rats; when the loops were arranged so that they filled but had difficulty in emptying, weakness, loss of weight, and steatorrhoea occurred. Unless these rather critical conditions are fulfilled, an intestinal abnormality will not cause malabsorption.

Normally, certain bacteria in the intestine are capable of synthesizing various essential food factors, including the B-vitamins. When stagnation occurs in a blind loop it seems that other bacteria proliferate, reduce the population of synthesizing organisms, and acquire for their own use the essential food factors required by the host (Fig. 1). This hypothesis is supported by the ability of some antibiotics to reverse this process and give clinical improvement with correction of both the steatorrhoea and the macrocytic anaemia.

The association of macrocytic anaemia, steatorrhoea, and abdominal cramps in a patient who has had a previous operation should make the clinician consider a diagnosis of cul-de-sac syndrome; a good clinical

response to an antibiotic is strong evidence in support of this diagnosis (Fig. 2).

Given a reliable diagnosis, the cul-de-sac syndrome can be cured in the majority of patients by resection of the blind loop or diverticulum. The surgeon is faced with a more difficult problem if the bowel is the seat of massive diverticulosis; resection under these circumstances may perpetuate intestinal insufficiency by removing a critical length of small intestine.

FIG. 1.—Probable sequence of events resulting in a deficiency state in cul-de-sac syndrome.

FIG. 2.—Improvement in steatorrhea during treatment with neomycin in a patient with cul-de-sac syndrome (50 g. fat per day) due to previous entero-enterostomy for acute small-bowel obstruction.

The dangers of producing stagnant loops of intestine are now widely recognized, and it is likely that fewer cases of the cul-de-sac syndrome will occur. Surgeons are aware of the dangers of short-circuit operations, and prefer end-to-end anastomosis to side-to-side anastomosis. In the past, by innocently creating this malabsorption picture, they have provided opportunity for profitable studies on the pathogenesis of the megaloblastic anaemias and on the biosynthesis of vitamins in man.

Gastro-colic Fistula

Gastro-colic fistula, with its dramatic nutritional disturbances, may be regarded as a severe form of cul-de-sac syndrome. In a series of cases of gastro-colic fistula reviewed at the Mayo Clinic, 50% of patients were noted to have clinical evidence of avitaminosis (Atwater *et al.*, 1943). The condition occurs as a complication of gastro-jejunal ulceration or, rarely, from cancerous invasion between the stomach and colon. The belief that malabsorption follows loss of gastric contents directly into the colon has now been clearly disproved;

the concept that diarrhoea results from the introduction of colonic bacteria into the proximal jejunum has been substantiated by the relief afforded regularly by proximal colostomy and by the benefit which follows treatment with intestinal antibiotics—now one of the mainstays of pre-operative preparation.

Though successful closure of the fistula will cure the malabsorption state, the safe management of these patients depends on an intelligent appreciation of the inherent biochemical problems. Relatively simple biochemical techniques can be used to demonstrate the profound alteration in electrolyte and nutritional balance which may result from a fistula and to monitor the rapid improvement on adequate preoperative therapy; a synopsis of one of my own cases, previously reported in detail by Connell (1957), is illustrative.

A man aged 32 was admitted to hospital complaining of severe and malodorous diarrhoea, foul eructations, extreme loss of weight, abdominal distension, and loss of energy. He gave a history of gastro-jejunostomy done for pyloric stenosis seven years previously. A reduction in the plasma proteins to 50% of normal was consistent with the gross oedema and ascites; the results of thiamine and riboflavin saturation tests were in keeping with the observed clinical signs of vitamin-B deficiency—pellagra and angular stomatitis; a serum calcium level of 6.9 mg./100 ml. explained the marked motor hyperexcitability and positive Chvostek sign; a greatly reduced serum potassium level may have accounted for his mental aberrations and extreme lassitude. Pre-operative treatment with a high-protein diet, 1 pint (570 ml.) of plasma intravenously every alternate day, and intramuscular vitamin-B complex, together with control of his diarrhoea by means of hexamethonium and chlortetracycline, resulted in a return of the abnormal biochemical findings to normal before operation. Operation, in a now fit subject, presented no difficulty, and within one month of discharge from hospital the patient had gained 1½ stone (9.5 kg.) in weight and had already returned to full work. Three years after operation he was still symptom-free.

Massive Resection of the Small Intestine

The clinical and metabolic effects of massive intestinal resections are of practical importance now that the surgeon, confident in the reliability of supportive measures and the high standard of modern anaesthesia, is able to remove large segments of diseased gut. Fortunately, the surgeon to-day is interested in the study of such cases and so has been able to advance our understanding of the physiology of the small intestine. This attitude of surgeons will be greatly appreciated by their patients, who are likely to be more interested in their own nutritional status than in the technical achievement of resecting a record length of gut.

While resection of up to two-thirds of the small bowel is compatible with good health, resections of greater extent will almost certainly result in malabsorption; when less than 18 in. (45 cm.) of small intestine remains after resection, death from inanition is likely. This knowledge is of practical importance when the surgeon encounters multiple segments of Crohn's disease and has to choose between an extensive resection or the making of several entero-anastomoses, with the inherent dangers of blind loops.

The patient who recovers from a massive resection has to face a period of post-operative fluid and electrolyte loss from profuse diarrhoea, which may persist for two to three weeks. When this crisis has passed the emphasis shifts from fluid imbalance to nutritional disturbance. Despite an adequate food intake, the

passage of bulky fat-laden stools leads to rapid loss of weight. The absorption of protein and of carbohydrate is also impaired, but to lesser degree than that of fat. In the absence of treatment, vitamin deficiencies, hypocalcaemia, hypoproteinaemia, and anaemia may occur. Gradually, compensatory mechanisms assert themselves and halt this progressive starvation. The lowered body weight permits survival on reduced calorie requirements and reduces the demand for protein replacement; anatomical adaptation involving hypertrophy of the remaining small intestine and its mucosal villi augments absorption; the colon increases its ability to absorb water, amino-acids, and crystalloids; reduction in the rate of gastric emptying allows an increased time for contact between food and mucosal surface. This last form of adaptation is well illustrated by the following case-history.

In a man aged 40, massive intestinal strangulation in an internal hernia necessitated resection of the caecum and of the small bowel to within 3 ft. (91 cm.) of the duodeno-jejunal flexure. He developed the typical starvation-steatorrhoea syndrome. Six months after operation he noticed a sudden and striking improvement in his symptoms coincident with the onset of epigastric discomfort and occasional vomiting of retention type. He gave a previous history of duodenal ulceration and a clinical and radiological diagnosis of pyloric stenosis was made. The addition of a gastro-jejunostomy in this particular patient was clearly undesirable, and he was trained to perform nightly gastric lavage with half-strength saline; on this regime he continued in good health for about eight years. It is highly probable that the pyloric obstruction had improved intestinal absorption by promoting "drip feeding" from the stomach into the residual small intestine. An operation planned to produce a degree of pyloric obstruction in patients with insufficient small intestine is rational and worthy of further study.

Repeated haematological studies in patients having had extensive resection of the distal small bowel may shed light on the disputed site of absorption of vitamin-B₁₂. Recent experimental work in the rat suggests that the ileum is the chief site of absorption of this vitamin and that resection of this part of the gut predisposes to macrocytic anaemia (Booth *et al.*, 1957). The patient whose history is described above had a mild microcytic anaemia, but repeated examination of the peripheral blood and bone-marrow has not revealed any sign of a developing macrocytic anaemia; the entire distal small bowel was removed, and yet, almost nine years later, there is no evidence of vitamin-B₁₂ deficiency, and tests have shown satisfactory vitamin-B₁₂ absorption (intestinal continuity was restored by anastomosing the jejunum to the ascending colon). This may reflect either a species difference or the ability of the jejunum to assume the function of absorbing this vitamin.

Conclusion

While there has been substantial progress in our understanding of the physiology of the small intestine, our knowledge must still be regarded as rudimentary. However, cases showing varying degrees of malabsorption are by no means uncommon and an increasing number of research tools are becoming available for use in their study. The radioactive labelling of such food factors as vitamin B₁₂, iron, and fats, has already led to a fuller understanding of the absorption of these substances from the intestine. Biopsy of the small intestine (Shiner, 1956) permits a histological study of the mucosal pattern in various disease states; if it is employed before, during, and after specific therapy much new information should

be gained. This technique also provides adequate tissue for histochemical and electron-microscopical studies. A readily ingestible pill has now been devised which contains a small radio transmitter, capable of transmitting information about hydrogen-ion concentration, pressure, and temperature during its passage through the small intestine (MacKay and Jacobson, 1958). The challenge is clear; new techniques are available, and intensive study should result in significant progress.

REFERENCES

- Anderson, C. D., Gunn, R. T. S., and Watt, J. K. (1955). *Brit. med. J.*, **1**, 508.
 Atwater, J. S., Butt, H. R., and Priestley, J. T. (1943). *Ann. Surg.*, **117**, 414.
 Booth, C. C., Chanarin, I., Anderson, B. B., and Mollin, D. L. (1957). *Brit. J. Haemat.*, **3**, 253.
 Burge, H., and Clark, P. A. (1959). *Brit. med. J.*, **1**, 1142.
 Cameron, D. G., Watson, G. M., and Wits, L. J. (1949). *Blood*, **4**, 803.
 Connell, A. M. (1957). *Scot. med. J.*, **2**, 162.
 Duncan, I. B. R., Goudie, J. G., Mackie, L. M., and Howie, J. W. (1954). *J. Path. Bact.*, **67**, 282.
 Feggetter, G. Y. (1959). *Proc. roy. Soc. Med.*, **52**, 838.
 Fox, H. J., and Grimson, K. S. (1950). *J. Lab. clin. Med.*, **35**, 362.
 Lundh, G. (1957). *Acta chir. scand.*, **113**, 431.
 MacKay, S., and Jacobson, B. (1958). *Electronics*, **31**, Jan. 3, p. 51.
 Meurling, S. (1953). *Acta Soc. Med. upsalien*, Suppl. 3.
 Poulley, J. W., Fairweather, F. A., and Leeming, A. (1957). *Lancet*, **1**, 406.
 Shiner, M. (1956). *Ibid.*, **1**, 17.
 Watson, G. M., and Wits, L. J. (1952). *Brit. med. J.*, **1**, 13.
 Welbourn, R., Hughes, R., and Wells, C. (1951). *Lancet*, **1**, 939.
 Wollaefer, E. E. (1950). *Postgrad. Med.*, **8**, 251.

POST-PUBERTAL ADRENAL VIRILISM WITH BIOCHEMICAL DISTURBANCE OF THE CONGENITAL TYPE OF ADRENAL HYPERPLASIA

BY

R. V. BROOKS, Ph.D., F.R.I.C.

D. MATTINGLY, M.B., B.S., M.R.C.P.

IVOR H. MILLS, M.D., Ph.D., M.R.C.P.

AND

F. T. G. PRUNTY, M.D., F.R.C.P.

From the Department of Metabolic Diseases, St. Thomas's Hospital, and the Department of Chemical Pathology, St. Thomas's Hospital Medical School, London

That the adrenal cortex could be the seat of lesions resulting in virilizing changes was first established by Bulloch and Sequeira (1905); the cases with which they were concerned were prepubertal. In 1910 Apert reviewed the available material, and developed a classification involving all age-groups which is the basis of that in use to-day. He was responsible for the present term "adrenal virilism," while the term "adreno-genital syndrome" derives from Gallais (1912). The syndrome was intensively studied by Broster and Vines (1933) prior to the second world war. It is apparent that the terminology used in the classification of these conditions has become confused. Thus the term "adreno-genital syndrome" may include cases of virilism arising before or after puberty and cases of the Cushing type (Broster, 1953). On the other hand, Wilkins (1957) properly makes a sharp distinction between the adreno-genital syndrome and Cushing's syndrome, including them under the term "hyper-adrenocorticism."

Though similar clinical changes may be brought about by adrenal cortical tumours or adrenal cortical "hyperplasia" the present paper is restricted to a