Current Practice

DISEASES OF THE DIGESTIVE SYSTEM

Malabsorptive States after Gastrointestinal Surgery

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One of the features of human physiology is the reserve capacity which is built into all the vital systems. This is nowhere more true than in the processes which together constitute digestion and absorption of food. It is not surprising, therefore, that before clinical syndromes of malabsorption become apparent several factors must come together at one and the same time. To give an example, the patients who lose weight after gastrectomy are often those who for one reason or another have an inadequate food intake, which when added to the malabsorption consequent upon their operation is sufficient to throw them into nutritional deficit.

Digestion begins in the mouth and proceeds in the stomach and small bowel. Therefore in order to clarify this subject a simple anatomical classification with surgical pathological states as sub-headings has been adopted in this paper.

Mouth

The mouth is an often-neglected area which by itself rarely, if ever, is solely responsible for malabsorption. But bad or completely absent teeth when combined with a deficient diet and, say, a gastrectomy may tip the balance of absorption from a healthy positive to a long-continued negative. The patient in this category is well known: the old man or woman struggling with only one or two teeth in a spasmodic nose-to-chin juxtaposition while chewing a crust of bread. Dental clearance and false teeth often result in dramatic improvement.

Stomach

Gastrectomy

Total gastrectomy results in a profound decrease in the ability of the patient to digest food. Added to this is the complete loss of intrinsic factor with resulting inability to absorb dietary vitamin B₁₂. These patients all require supplementary vitamin B₁₂, which is best administered as an intramuscular injection at a dose of 250 µg. per month. This therapy will provide absolute protection against macrocytic anaemia (assuming folic acid absorption to be normal), and is necessary even though the body's reserves of B₁₂ are usually sufficient to maintain normal haemopoiesis for two to five years.

The remaining digestive alterations are similar to, but more severe than, those seen after partial gastrectomy.

Partial gastrectomies fall into one of two main categories. In the first are those gastrectomies which result in the food being diverted away from the duodenum, and in the second are those in which this does not happen (see Figs. 1 and 2). This distinction

between the different types of gastrectomy has been made because when the duodenum is "out of circuit" the mixing of the gastric chyme, bile, and pancreatic and intestinal juices occurs in the wrong order and the nervous and hormonal integration of this mixing is less efficient. In addition the major site of absorption for iron and calcium and possibly magnesium is in the duodenum, and thus bypass adversely affects their absorption (Fig. 3).

FIG. 1.—Operations which result in bypassing of the duodenum.

FIG. 2.—Operations which do not result in bypassing of the duodenum.

Loss of the reservoir capacity of the stomach, common to all gastrectomies, results in less efficient churning and mixing of the ingested food. In addition the pH of the stomach is higher than normal by virtue of loss of acid-secreting parietal cells. Both these effects result in the discharge of gastric chyme which is less well digested than normally into the small bowel. These then are the theoretical considerations to be taken into account when discussing the effect of gastrectomy on absorption. What are the known effects of these operations on individual nutrient materials?

Glucose or other more complex carbohydrates are fully absorbed following any kind of gastrectomy provided that the small bowel is normal.

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Fat absorption, a more complicated process, depends on hydrolysis of the fat by lipases into its constituent fatty acids, mono- and di-glycerides and glycerol. This process is accelerated to physiological speeds by the formation of a micellar solution of the fat-soluble products of digestion, mainly β -monoglycerides and fatty acids, by bile salts. Steatorrhoea—that is, a daily faecal fat excretion in excess of 7 g. per day—nearly always follows total gastrectomy, is very common after the Polya type of gastrectomy, and is less common after the Billroth I gastrectomy. It is interesting to note that the degree of steatorrhoea in the Polya operation depends to some extent at least on the length of the afferent loop.

FIG. 3.—Sites of absorption.

Steatorrhoea by itself is of little significance, but it produces as secondary phenomena loss of calcium and magnesium in the form of insoluble soaps, and if very severe can even lead to significant loss of sodium and potassium. In addition it indicates that the fat-soluble vitamins, in particular vitamin D, are also being poorly absorbed. Perhaps the most significant effect in the post-gastrectomy state is the slight but persistent negative calcium balance, which when occurring over many years may result in osteomalacia. These changes rarely become manifest less than five years after operation, but must always be borne in mind in a patient who develops pain in the bones, possibly associated with a kyphosis. The diagnosis may be made on the basis of a low serum calcium and phosphate, raised alkaline phosphatase, the presence of Looser's zones or pseudo fractures in the bones, increased thickness of the osteoid seams as judged from a bone biopsy to greater than 15μ in width, and a positive response to vitamin D. Although osteomalacia is generally uncommon after gastrectomy an elevated alkaline phosphatase, which is the most useful screening test, was found in nearly one-quarter of one series of patients. If the condition is proved, therapy is with vitamin D and calcium. In patients in poor nutritional condition after gastrectomy prophylactic treatment should be given with one daily tablet of calcium with vitamin D, B.P.C. (calcium sodium lactate 500 mg., calcium phosphate 150 mg., vitamin D 500 units). It is possible for osteoporosis to coexist with osteomalacia in these patients and it has been suggested that, since it is difficult to distinguish these conditions, they should be considered together as "postgastrectomy bone disease."

Iron is not absorbed so readily following gastrectomy. It is hardly surprising, therefore, that anaemia, which is usually iron deficient in type, has been found to occur in up to 30% of cases five to six years after a Polya type of gastrectomy. The

diagnosis is made by estimating the haemoglobin, and screening for the type of anaemia is most rapidly achieved by examination of a blood film. However, the diagnosis is confirmed by estimation of the serum iron and the more reliable index, the total iron-binding capacity of the serum. If the total iron-binding capacity rises above $400\text{--}420\text{ }\mu\text{g./100 ml.}$ of blood regardless of haemoglobin or iron, this is strongly suggestive of iron deficiency. Women, particularly in the reproductive years, are more prone to develop iron-deficiency anaemia than are men, and therefore constitute a group of patients who require most careful follow-up after operation. There is some controversy on whether it is possible to be in an iron-deficient state in the presence of a normal haemoglobin. Certainly symptoms such as tiredness may improve on oral iron therapy even though the appearance of the peripheral blood is normal. Perhaps the best advice in this respect is that most patients, and certainly those in poor nutritional condition, women, and those whose operations have resulted in duodenal bypass, should receive a one month's course of oral iron per year.

Vitamin B_{12} deficiency is a rare complication of partial gastrectomy, occurring in only 1% to 2% of cases, and always several years after operation. Clinically these patients have pernicious anaemia with anorexia and weight loss, together with soreness and smoothness of the tongue. If neglected the picture can even proceed until the neurological signs of subacute combined degeneration of the cord become apparent. The diagnosis is suspected from the appearance of a blood film and confirmed by marrow examination and the finding of a low serum vitamin B_{12} . Therapy, which must only follow accurate diagnosis, is to saturate the B_{12} stores with $1,000\text{ }\mu\text{g.}$ of B_{12} weekly for four weeks followed by a maintenance dose of $250\text{ }\mu\text{g.}$ by intramuscular injection monthly.

Folic acid deficiency is even more rare, occurring in probably under 1% of patients after partial gastrectomy. The clinical presentation is glossitis, weight loss, and diarrhoea. Diagnosis is by examination of a blood film and estimation of serum folic acid, which will be below the normal range, which is down to 2.1 ng./ml. of blood. Therapy is with oral folic acid, 20 mg. daily.

Protein digestion and absorption is reduced after gastrectomy. After total gastrectomy up to 50% of patients excrete more than 2.5 g. faecal nitrogen per day, which is the upper limit of normal. The percentage of patients with raised faecal nitrogen excretion after the Polya type of operation is smaller, and is probably only in the region of 10–20%. It is likely that even fewer patients after the Billroth I type of operation suffer this defect. It is probable that patients who suffer persistent excessive nitrogen loss are those in whom there is other evidence of absorptive defects such as weight loss, general malaise, and anaemia. Their protein deficit is best made up by increasing protein intake.

Vagotomy and Gastric Drainage

Vagotomy may be either total or selective, but at present there is no evidence that preservation of the extragastric vagal nerve fibres confers any nutritional advantage. The gastric drainage operation, which is essential after any form of vagotomy, may be either a gastrojejunostomy, which results in bypass of the duodenum, or a pyloroplasty, which does not (Figs. 1 and 2). The nutritional deficit after either of these operations may be considered in the same way as those that occur after gastrectomy. However, less information has been published about the long-term effects of these operations, and so they will be considered together.

Following vagotomy and gastrojejunostomy there is a tendency for the patient's weight to be adjusted to a level just below that which could be considered ideal by height, sex, and age. Thus if a patient is far below the normal weight at the time of operation weight will be gained subsequently. The

converse is also true, and a patient who is overweight at operation tends to lose weight postoperatively. The same is probably true for the weight changes which occur after vagotomy and pyloroplasty, but the evidence that exists suggests that the weight deficit after operation is less than that for the gastrojejunostomy type of drainage.

As with gastrectomy, there is no evidence of malabsorption of carbohydrates after vagotomy and drainage.

Some increase in faecal fat excretion occurs after vagotomy and drainage in most patients and to above 7 g. per day in about half. It has not been shown that gastrojejunostomy results in greater fat excretion than pyloroplasty, even though this would be expected on theoretical grounds.

The significance of a raised faecal fat excretion is the same as for gastrectomy. But no cases of osteomalacia or osteoporosis following vagotomy and drainage have yet been reported. These changes take many years to develop, however—probably more than 10—and vagotomy is a relatively recent innovation.

Some patients probably become anaemic after vagotomy and gastrojejunostomy, but those that do are those patients who were anaemic before the operation as well. The serum iron has been shown to fall after this operation, both in men and women, and this suggests that even though the development of anaemia is not so certain as after gastrectomy these patients will benefit from one month's oral iron therapy per year. The information relating to iron-deficiency anaemia following vagotomy and pyloroplasty is at present sparse, but it seems to be an uncommon late complication of this operation.

Depressed vitamin B₁₂ absorption after vagotomy and gastrojejunostomy has been demonstrated by the Schilling test in a small percentage of patients, but no case of megaloblastic anaemia has been reported. Serum folate levels after vagotomy have so far been within the normal range.

Pancreas

Total pancreatectomy, as performed for some carcinomas of the pancreas or the terminal biliary duct system, naturally results in complete loss of both pancreatic exocrine and endocrine function. The proteolytic enzymes and the amylase are adequately compensated for by the enzymes found in succus entericus. Pancreatic lipase, however, is essential for complete fat digestion and absorption. Gastric lipase has been described, although its existence is controversial, and there is certainly some small-bowel mucosal lipase. However, the contribution that both these sources make to the hydrolysis of ingested fat is small, and consequently loss of pancreatic lipase results in an increase in the amount of fat excreted. Another factor affecting fat digestion in these cases is the anatomical rearrangement involved in the operation. A common method of reconstruction following radical pancreatoduodenectomy is to join the divided common bile duct to the upper end of a loop of jejunum which is itself then anastomosed end to side to the remaining two-thirds of the stomach. Consequently here again is seen the effect of inefficient mixing of bile and gastric chyme before entry into the small bowel. The increase in fat excretion is variable between individuals, but on average amounts to some 25% of that ingested. With average dietary intake this results in a faecal fat excretion in the region of 25 to 30 g. per 24 hours. Clinically this results in bulky, fatty, and offensive stools nearly always associated with diarrhoea. These patients lose weight as a rule, and without adequate prophylaxis they later develop osteomalacia.

Replacement therapy with tablets of dried pancreas (pancreatin 0.5 to 3 g. daily) may be given, but this is not usually adequate by itself to reduce the fat excretion and calcium loss to normal. Of greater importance is limitation of the intake of fat to approximately 30 g. per day. It is quite possible to arrange a palatable diet with this amount of fat, and as a result the faecal fat will fall to much lower levels. In addition to

reduction of the calcium and magnesium loss the diarrhoea is also improved. Supplementary vitamin D is required, and once again may conveniently be prescribed together with calcium as calcium with vitamin D tablets, B.P.C. As well as these specific supplements it is usual to add the other vitamins in capsule form and iron to the diet.

Small Bowel

Intestinal Resection.—Loss of small bowel results in loss of absorptive area, but the effect of this depends on which part or parts of the bowel are removed. In general terms absorption by the small bowel depends on specific transport mechanisms, the transit time, and the speed with which a particular food material is absorbed. The jejunum has a rapid transit time—often only 10 to 15 minutes—whereas the ileum slows the passage of its contents so that transit takes up to two hours. Glucose, iron, folic acid, riboflavine, pyridoxine, and ascorbic acid are rapidly absorbed in the jejunum. Proteins and fats, however, are not completely absorbed until the ileum is reached. Thus, loss of various parts of the small bowel produces widely different effects.

Vitamin B₁₂ is absorbed by the terminal six feet (2 m.) of ileum, and if this section is lost—for example, by resection for granulomatous ileitis—replacement therapy will be required. The dose and frequency of administration are as described following total gastrectomy. Apart from this there is no other effect on absorption.

If most of the terminal ileum is resected, one of the main results will be a reduction in small bowel transit time, with reduced fat and protein absorption as well as the inability to absorb vitamin B₁₂ already mentioned. In this case the predominant symptomatology is that of diarrhoea with steatorrhoea. The symptoms can be improved by reducing fat intake while maintaining a high protein intake. In spite of the considerable steatorrhoea the fat-soluble vitamins are usually adequately absorbed and so supplements are not required.

If still more small bowel is lost, including all the ileum and most of the jejunum, this situation is still compatible with life. Several cases are recorded in which only seven or eight inches (about 20 cm.) of jejunum remain, and even one remarkable case in which the whole of the jejunum and ileum and right colon was removed with survival. However, when only small lengths of jejunum are left small bowel transit time is reduced to a minimum and these patients suffer extreme diarrhoea with dehydration, steatorrhoea, and azotorrhoea. The dietary measures that can be taken include giving a low fat diet so as to minimize loss of calcium, magnesium, and in extreme cases sodium and potassium, which the steatorrhoea causes. Supplements of all vitamins are required, together with added calcium. A surgical approach to this problem has been the use of reversed segments of intestine so as to produce a slowing in the passage of the bowel contents. A segment of the small bowel, usually between three and six inches in length, is excised with preservation of its vascular pedicle. It is then rotated through 180° and re-anastomosed, end to end, back into its former situation, but with the difference that now it forms an anti-peristaltic segment. By using this means both diarrhoea and steatorrhoea have been successfully reduced.

Proximal resections of jejunum produce remarkably little effect in terms of both symptoms and absorption. If the ileum is left intact it seems able to assume the functions of the jejunum, presumably because the slower transit along it allows time for the absorption of the small bowel contents normally occurring in a more proximal situation.

Blind Loop Syndrome.—This condition is characterized by diarrhoea, steatorrhoea, anaemia, and loss of weight. There may be associated abdominal pain and multiple vitamin deficiencies. It is due to a blind loop or loops occurring in the small bowel, and it is worth pointing out that a blind loop may

be any pouch which results in stasis of intestinal content—for example, a jejunal diverticulum whose wall does not possess muscle and cannot therefore empty, or a stricture of the small bowel. Certain surgical procedures result in the formation of blind loops—for example, a side-to-side anastomosis in which either a small non-emptying pouch or, in the case of an intestinal bypass, a large relatively stagnant loop is produced.

Diagnosis is achieved by performing a Schilling test both without and then with added intrinsic factor. If the latter test gives a similar result to the former then this is unlike true pernicious anaemia, since intrinsic factor would increase the absorption of vitamin B₁₂. Tetracycline is now given for five days and the Schilling test is repeated. In the blind loop syndrome the test will have returned to normal limits.

Treatment is by surgical removal of the loop if feasible; otherwise it is by giving antibiotics to change the flora in the loop.

Intestinal Fistulae

These are quite rare, but nevertheless when they do occur can occasionally cause malabsorption. The precise effects depend upon which part of the intestine is left out of circuit. Naturally the greater the length of bowel bypassed the greater is the nutritional deficit, an added complication in some cases being the development of a blind loop syndrome.

Treatment is generally surgical, and is aimed at closing the fistula if this is possible, together with removing the cause. For example, in the case of a gastro-jejuno-colic fistula, usually due to a recurrent peptic ulcer, careful closure of the fistula together with vagotomy will be curative. The more difficult problems are posed by inflammatory diseases of the bowel—for example, granulomatous ileitis—when not only do multiple fistulae form

in an inflamed area but even when the affected section of bowel is resected that which remains is often abnormal. However, the more small bowel mucosa that can be brought into contact with the food stream the less is the absorptive defect.

Conclusions

An attempt has been made in this paper to outline those malabsorptive states which occur as the result of surgery or are amenable to surgical treatment. It is perhaps well to remember that the most common cases of malabsorption are iatrogenic—that is, they occur after gastric surgery—and are amenable to no more complex therapy than slight adjustment or increase in the diet.

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TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Drugs for Tuberculosis

Isoniazid, streptomycin, and para-aminosalicylic acid (P.A.S.) are the standard drugs used for the initial optimal chemotherapy of tuberculosis.

Isoniazid

Isoniazid (isonicotinic acid hydrazide) takes pride of place among the antituberculosis drugs, since it is unique in combining high potency, remarkable lack of toxicity, and cheapness. Given orally it is rapidly and well absorbed, widely distributed in the tissues, penetrates well into pleural and cerebrospinal fluids, and is active against intracellular mycobacteria. The rate of isoniazid inactivation is a genetically determined phenomenon and varies between individuals and races. About a third of Caucasians are rapid inactivators.

Toxicity.—Peripheral neuritis is dose related. It is exceedingly rare with conventional dosage (4 to 5 mg./kg.), except in patients with renal impairment or vitamin-B deficiency. Doses of 10 mg./kg. or more result in peripheral neuritis in about a fifth of patients, particularly among the slow inactivators. The neuritis is associated with pyridoxine deficiency, and when such large doses are used pyridoxine 10 mg. daily should be given prophylactically. Toxic psychoses and epilepsy are very rare.

Therapy.—A daily dose of 300 mg. (4 to 5 mg./kg.) in one or two doses is an effective dose when given with daily streptomycin or P.A.S. or both. There is no evidence that rapid inactivators require more or that larger doses produce better results in combined therapy.

Streptomycin

Streptomycin was discussed in a recent article in this series ("Today's Drugs," 3 August, p. 299).

Therapy.—The standard dose of streptomycin sulphate is 1 g. in a single dose, but either 0.75 g. daily or 1 g. three times weekly is generally recommended for patients over 40 years because of the increased risk of vestibular damage in middle age. In patients with renal impairment or in the elderly doses should be adjusted according to streptomycin blood levels, so that the serum level 24 hours after injection does not exceed 1 µg./ml. Streptoduoicin, a mixture of equal parts of dihydrostreptomycin and streptomycin, is less likely to cause vestibular symptoms than streptomycin, but is more likely to cause irreversible deafness, and for this reason is not recommended for general use. In children streptomycin is given in a dose of 30 mg./kg. Little streptomycin enters the cerebrospinal fluid, but intrathecal therapy is usually unnecessary in tuberculous meningitis. Streptomycin diffuses freely into the pleural fluid, so intrapleural streptomycin is generally unnecessary.

Para-aminosalicylic Acid (P.A.S.)

P.A.S. is used as a "companion" drug to isoniazid and streptomycin to prevent the emergence of resistance to these