THE DIGESTIVE SYSTEM

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their management is entirely different. In patients who have reflux, esophagitis, ulceration and fibrosis occur. The early stages of postcardiomyotomy reflux are apt to be overlooked, because it is difficult to demonstrate such reflux radiologically or endoscopically, and patients who have been relieved from dysphagia are apt to ignore more moderate symptoms of another type.

Frank Ellis and F. L. Cole[3] (Guy's Hosp., London) studied the incidence, causes and effects of reflux after cardiomyotomy in 53 patients who had been treated an average of 8 years previously (range 2-20). In most, a long, single anterior myotomy had been performed. Clinical and x-ray evaluation was carried out by two observers each of whom was unaware of the other's findings.

The radiologic detection of reflux by usual methods was difficult, because barium suspension tended to remain in the esophagus and interfered with visualization of reflux. This difficulty was overcome by giving the patients about a third of a liter of water to drink. When the esophagus had been so cleared of barium, the patient was placed head down, and external pressure over the stomach was applied with the patient both supine and prone. Some patients had to be kept head down for 10 minutes before there was evidence of a slow, trickling type of reflux.

Clinical symptoms suggested esophagitis in 17 patients, and 16 were found to have reflux on x-ray examination. These two groups, however, did not consist of the same patients: among 30 patients without reflux, 8 had heartburn and regurgitation; and among 16 having reflux, 7 had no symptoms. Of the 9 having both reflux and symptoms, 4 had gross strictures. These findings suggest that heartburn and regurgitation, the usual hallmarks of gastroesophageal incompetence, are not reliable indicators of reflux in patients who have had a cardiomyotomy for achalasia. It was further apparent that there is no substitute for careful radiology in the proper evaluation of the gastroesophageal junction after cardiomyotomy.

In an attempt to analyze factors that might predispose to reflux, it was found that 4 patients had had a more extensive type of Heller procedure than is considered optimal, 2 had been subjected to previous sphincter-destroying operations, 2

(3) Gut 6 80-84, February, 1965

had had duodenal ulcers, 1 had had a pneumonectomy and 1 had a hiatus hernia. Four of the 9 patients with both symptoms and x-ray evidence of reflux had been managed adequately with antacids, but the 5 others had required further operation, which, except in 1 had also been unsuccessful.

The surgical treatment of achalasia faces a dilemma, for any procedure that provides adequate esophageal drainage may so lower the competence of the gastroesophageal sphincter that reflux is inevitable. This dilemma may be in part circumvented by careful selection of patients and attention to detail during operation. That 2 of the patients with esophagitis after cardiomyotomy had had duodenal ulcer suggests that the preoperative examination should include studies of gastric acidity. Cardiomyotomy should not be lightly undertaken in patients who have duodenal ulcer or high gastric acidity.

Although a long myotomy incision is advisable to afford adequate esophageal drainage, the incision should be extended down on the lesser curvature of the stomach, thus avoiding the oblique muscle sling of Helvetius, which helps maintain the mucosal rosette at the gastroesophageal junction Care must also be taken to preserve the hiatal mechanism, which may be weakened by excessive mobilization of the esophagus, division of the phrenoesophageal ligaments, displacement of the stomach into the chest and failure to restore the lower segment of the esophagus to its position below the diaphragm. Further, avoidance of damage to the vagus is imperative, because postoperative gastric retention may result in reflux

[The authors' statement that "clinical evaluation on the basis of history gives little idea of what is really going on in terms of reflux and its potential deleterious effect" may well be compared with the diametrically opposite opinion expressed in the article by Edwards and his associates (see p 352). —Ed.]

Hiatus Hernia and Diverticulum of Colon: Their Low Incidence in Korea is emphasized by Eung Ho Kim[4] (Catholic Med College, Seoul). A prospective study of 1,000 consecutive barium meal examinations was carried out to detect hiatus hernia The number of males and females was about equal, and the series comprised more than 200 patients in each of the 4th, 5th and 6th decades. Patients were studied in the prone right anterior position with the left side moder-

ately elevated and with a mat placed under the upper abdomen Spot films were taken during barium swallows on deep inspiration, during expiration and during quiet breathing Minimal herniation was diagnosed when notches indicating the distal margin of the gastroesophageal vestibule were seen above the diaphragm and a barium column more than 2.5 cm. in diameter was demonstrable in the hiatal area. If the notches were more than 3 cm. above the diaphragm, herniation was defined as moderate.

According to these criteria, 14 cases (1.4%) of minimal hiatus hernia were noted, and 11 of these were found in patients over age 50 years. All hernias were classified as sliding; no case of paraesophageal hernia was encountered

Esophageal diverticula were noted in 0.8% of patients examined and duodenal diverticula in 1.5%. In 500 barium-enema examinations analyzed retrospectively, diverticulosis of the descending colon was never found, and only 1 case of a single small diverticulum (on the medial aspect of the ascending colon) was seen in the whole group.

The low incidence of hiatus hernia found in Korea is to be compared with the figure of 8-50% usually cited in the American and European literature. The reason for this difference is not clear, but it is probably a matter of racial background rather than one dependent on dietary or living habits

► [The criteria used in diagnosing hiatal herniation of the stomach are a matter of dispute and may differ considerably from one radiologic department to another Yet, even if allowances are made for this fact, it is striking that no large hernias which anyone could recognize, and in particular no paraesophageal hernias, were noted in this entire series Thus, the evidence convinces me that hiatus hernia and colonic diverticulosis have a much lower incidence in Koreans than they do in the United States' population Our total ignorance as to what predisposes so many of our older people to these conditions lends particular interest to the findings here reported – Ed]

Clinical and Radiologic Results of Repair of Hiatus Hernia were assessed by D. A. W. Edwards, S. F. Phillips and E. N. Rowlands[5] (London) The clinical material consisted of 63 patients (46 females) who had been treated surgically for 60 sliding and 3 paraesophageal hernias. The operations consisted of simple repair of the hernia with suture of the hiatus behind the esophagus in 36; in 23 vagotomy with a drainage procedure was carried out besides hernia repair. The procedures in the rest were variable or not described. Indications for operation were failure of medical therapy in 54 patients and bleeding in 9. After a postoperative interval ranging

(5) Brit M J 2 714 718, Sept 19, 1964

from less than a year to 11 years, 37 patients were interviewed and radiologically examined by the authors, none of whom had ever seen the patients before; for the others, data were obtained from record review or questionnaire. Those radiologically examined by the authors were subjected to a standard technic in which the patients were examined in various positions while lying with the head slightly lower than the feet but without application of abdominal pressure.

Fifty patients were pleased with the outcome of the operation. Six denied any symptoms, but 42 still had occasional mild symptoms of reflux. The other 2 had moderately severe reflux symptoms but were much improved over their preoperative states. Among this satisfied group were 19 patients with some form of dysphagia (in 2 of these esophageal stricture developed postoperatively), 5 with postvagotomy diarrhea, 1 with bilious vomiting from an afferent loop syndrome and 1 with dumping. Twelve patients did not believe the operation had been worthwhile, because the symptoms of reflux had been insufficiently relieved. The incidence of dissatisfied patients did not appear to be related to duration of follow-up.

When the postoperative status was evaluated in terms of the preoperative symptoms of substernal pain, heartburn, regurgitation, vomiting, dysphagia and excessive belching, the operation was found to have relieved substernal pain and heartburn in 90% of patients and regurgitation and vomiting in 77%. Some were relieved from dysphagia, but others, who had not had it previously, acquired this symptom.

Of 45 patients with adequate radiologic follow-up, 17 had neither hernia nor reflux, 13 had reflux but no hernia and 15 had both. Comparison of clinical and x-ray results showed that 36 of this group of 45 patients thought that the operation had been worthwhile, but only 13 of these 36 had neither hernia nor reflux on x-ray examination. Twelve had reflux without hernia. Further, there was some discrepancy between the clinical and radiologic evidence of reflux, for slight reflux was found in 3 of 4 patients who had no symptoms postoperatively, and no reflux was demonstrated in 12 who had symptoms suggesting this disorder. By and large, neither the clinical results nor the x-ray findings appeared to be affected by the type of operation performed.

This study emphasizes that many patients treated surgically

and 15 mN sodium chloride with similar concentrations of D_2O and Na^{24}. Heidenhain pouches were tested, at rest, while secreting acid and before and after topical application of a solution of eugenol, an irritant that renders the mucosa readily permeable to sodium

The volume of the pouch secretory response to an injection of histamine was not changed by prior application of eugenol However, the concentration of hydrogen ions was greatly decreased and that of sodium ions increased in a reciprocal manner, indicating either that the barrier to sodium had been disrupted or that the parietal cells had secreted sodium chloride instead of hydrochloric acid. The change in the composition of the test fluids instilled into the pouches showed that the former explanation was correct. Thus, after the application of eugenol, net transmucosal movements of sodium, hydrogen and potassium were increased seven- to 13-fold. In particular, the movements of sodium into the lumen and of hydrogen out of the lumen were increased, these movements suggesting an exchange of these ions. This exchange was accompanied by a small increase in intraluminal potassium but little net change in chloride. The movement of water was unaffected by treatment with eugenol

In the next set of experiments, the test solutions were placed in pouches and histamine was administered. When no eugenol had been given, histamine stimulation caused a large accumulation of hydrogen ions in the pouch whether the solution in the pouch was acid or glycine. After eugenol treatment, no accumulation of hydrogen ions followed histamine stimulation when the solution in the pouches was acid. In contrast, when glycine solution was used, glycine trapped these hydrogen ions, and the acid accumulating in the pouch approached that observed without eugenol. Therefore, when the mucosal barrier to sodium and hydrogen ions was broken by eugenol, the mucosa was still able to secrete acid in response to histamine. In the presence of the acid, nonbuffering solution, however, the secreted hydrogen ions rapidly left the lumen through the altered mucosa and exchanged with sodium ions that entered the lumen.

The potential difference across the gastric mucosa of the pouch had a mean value of 39.4 mv. ± 18.8 (S.E.M.), with the mucosa negative with respect to the reference electrode placed in a vein. Topical application of eugenol resulted in

prompt reduction of the potential difference, often to zero. In general, the largest potential difference was found with the smallest accumulation of sodium and vice versa. This effect was predictable, since a membrane that has become freely permeable to charged ions is not likely to maintain a separation of charges that creates a measurable potential difference.

These experiments show that under normal conditions hydrogen-sodium exchange does not play a major role in controlling the degree of intraluminal gastric acidity. When the gastric mucosal barrier is damaged, however, exchange diffusion is increased over the minute amount normally present, and control of intraluminal acidity is lost, irrespective of the continuing ability of parietal cells to secrete acid. Thus, the impermeability of the gastric mucosa is more closely related to the ability of the stomach to maintain a highly acid solution than to produce one. Parietal cells are needed to make acid, but the integrity of the entire mucosa is necessary for maintenance of acidity.

The Antral Hormone Gastrin. By chemical analysis of gastrin I and gastrin II isolated from natural sources, H. Gregory, P M. Hardy, D. S. Jones, G. W. Kenner and R. C. Sheppard[8] (Univ. of Liverpool) were able to identify the 17 amino acids making up these substances, as well as their sequence in the polypeptide chain. The structure of gastrin II is.

$$\text{L-Glu.Gly.Pro.Try.Mot.Glu.Glu.Glu.Glu.Glu.Ala.}\underset{\displaystyle SO_3H}{\underset{|}{\text{Tyr.}}}\text{Gly.Try.Met.Asp.Phe.}NH_2$$

and gastrin I differs from gastrin II only in lacking the sulfate ester group attached to the tyrosine fragments.

On the basis of this chemical analysis, J. C. Anderson, Moira A. Barton. R. A. Gregory, Hardy, Kenner, J. K. MacLeod, J. Preston and Sheppard[9] (Univ. of Liverpool) and J. S. Morley (Alderley Park) were able to synthesize the two gastrins as well as smaller peptides consisting of fractions of the entire gastrin molecule. Of such fractions, the final tetrapeptide sequence, tryptophan-methionine-asparagine-phenylalanine-NH_2, proved of particular interest.

The physiologic properties of a series of synthetic peptides

structurally related to gastrin I were studied by Hilda J. Tracy and R. A. Gregory[8] (Univ. of Liverpool) in the hope of localizing specific functions of gastrin in different regions of the total gastrin molecule. Pure natural gastrins I and II, when given in small doses, stimulate the secretion of a highly acid gastric juice containing little pepsin. Dependent on the size of the dose and the form of injection, the gastrins also may inhibit gastric acid secretion and may stimulate pepsin secretion, pancreatic secretion and the tone and motility of the stomach and small intestine. The motility of the biliary tract and blood pressure are not affected.

This entire range of physiologic activities displayed by the natural gastrins was found to be possessed by the terminal tetrapeptide sequence that had been synthesized, although the potency of the tetrapeptide did not equal that of the entire gastrin molecule. Other fractions of the gastrin chain exhibited some gastrin-like activity, but not the entire range of activities. Elimination of the terminal tetrapeptide sequence, and even elimination of the terminal amide group, produced compounds that had little gastrin-like activity.

► [Many feel that the fingerprinting of gastrin in terms of its amino acid sequence, and its synthetic production on the basis of this fingerprinting, constitute gastroenterologic advances of major magnitude. The theoretically possible applications of these achievements are many, but in particular they should enable the elucidation of the role of gastrin in the pathogenesis of peptic ulcer. It should prove possible to discover if and why patients with peptic ulcer produce gastrin excessively. It is even conceivable that immunologic or other technics might be used to produce an antigastrin. – Ed.]

Effect of Gastrin I and II on Secretion of Intrinsic Factor. W. J. Irvine[9] (Royal Infirm, Edinburgh) gave intramuscular injections of gastrin isolated from hog antrum mucosa (no histamine activity was detectable) to 1 normal human subject, 1 with moderate gastritis, 1 with achlorhydria and atrophic gastritis and 1 with pernicious anemia. The first 3 had normal vitamin B_{12} absorption. On another day, the same subjects were given maximal injections of histamine. The collected gastric samples were titrated for acidity and also for intrinsic factor content by an immunoassay using a serum with a high titer of antibody to intrinsic factor.

In the normal subject, both histamine and gastrin produced a five- to sixfold increase in intrinsic factor content of the basal gastric juice. After gastrin, the peak intrinsic factor output occurred within 20 minutes and after histamine at

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20-40 minutes. The acid output in this subject was somewhat greater after histamine than after gastrin injection. Similar results were found in the patient with moderate gastritis, but in the patient with severe gastritis, the gastrin-induced output of intrinsic factor was chronologically diffuse and considerably less than that elicited by histamine. In the patient with pernicious anemia, only trace amounts of intrinsic factor appeared after either gastrin or histamine injection. Thus gastrin is about as effective as histamine for stimulation of secretion of intrinsic factor by the human stomach.

▻ [This report lists still another effect of gastrin in addition to those listed by Gregory and his associates (see preceding article) An interesting feature is that histamine, which certainly stimulates the parietal cell predominantly, and gastrin both increase the output of intrinsic factor, thus providing additional support for the currently developing belief that intrinsic factor may come from parietal cells after all - Ed.]

Antacid Therapy of Peptic Ulcer.—*I. Mathematical definition of adequate dose* —J. Myhill and D. W. Piper[1] (Univ. of Sydney) derive a formula based on the three variables involved, gastric secretion, gastric emptying and the neutralizing capacity of antacids. The purpose of the formula is to determine the amount of excess antacid (r_0) that must be present at the time (τ) when the stomach starts to empty exponentially to insure that at any given later time (T) no deficiency of antacid will occur. The formula is

$$r_0 = \frac{s}{\kappa}(e^{\kappa\tau} - 1 + \tau\kappa)$$

where s is the rate per unit time at which antacid is neutralized by acid secreted by the stomach, κ is the emptying rate constant of excess antacid and e is the base of the natural logarithm.

To determine the quantity of antacid needed to treat a given patient, his rates of gastric secretion and gastric emptying would have to be known. In many patients the rate of basal gastric secretion can be measured, but determination of emptying rate is laborious. In the absence of information concerning individual secretory and emptying rates, calculations may be based on ranges available in the literature concerning rates of gastric emptying and of gastric secretion in men or women with gastric or duodenal ulcer. Calculations so derived permit definition of the dose of ant-

[1] Gut 5 551 560, December, 1964

TABLE 1 — PERCENTAGE OF PATIENTS WITH VARYING SECRETORY RATES ADEQUATELY TREATED BY ANTACID DOSES OF 25 AND 50 MEQ ADMINISTERED HOURLY

Secretion Rate (mEq /hr)	*Percentage Adequately Treated by Hourly Antacid Dose of*	
	50 mEq	*25 mEq*
1 0	98 8	97 7
5 0	93 8	79 3
10	78 9	31 0
15	54 8	5 5
20	31 2	1 0
25	13 6	1 0
30	5 7	< 1 0
Male duodenal ulcer	90 0	66 2
Female duodenal ulcer	96 0	88 6
Male gastric ulcer	97·0	88 2

acid that will reduce gastric acidity to zero in any desired fraction of patients being treated, e.g , the dose that will adequately treat 90% of patients can be established

To determine r_0, i.e., the antacid dosage needed to treat any desired fraction of patients, the distribution of this dosage was determined for 1,000 hypothetical patients by means of the foregoing equation and by using random sampling values of κ, τ and s in the equation. On the basis of this mathematical treatment, the amount of hourly antacid necessary to treat 90% of male duodenal ulcer patients adequately is found to be 50 mEq., for female duodenal ulcer patients, the figure is 27 mEq. and for male gastric ulcer patients, it is 26 mEq. The amount of antacid needed when the patient's basal secretory rate is known is shown in Table 1. Roughly, a dose of neutralizing capacity 8 times the secretion rate should suffice in most instances. The efficacy of treatment is grossly influenced by the frequency of administration of the antacid. Thus much smaller doses are required if the antacid is administered continuously, whereas doses administered every 2 hours or less frequently involve amounts of antacid over a 12-hour period that are impractical in all but patients with the lowest gastric secretory rates.

These calculations, it is to be emphasized, apply to a group of patients, e.g., 90% of males with duodenal ulcer, and not necessarily to a given patient. They do not take into account the secretory response to frequent meals that may

TABLE 2 – NEUTRALIZING CAPACITY OF SERIES OF ANTACIDS AT 0, 5, 10 AND 30 MINUTES AND 2 HOURS MIXING

Antacid (1g)	*Neutralizing Capacity (ml $N_{10}HCl$) (time after mixing in min)*					*Neutralizing Capacity (ml $N/_{10}HCl$) (time after mixing in min)*				
	0	*5*	*10*	*30*	*120*	*0*	*5*	*10*	*30*	*120*
Powders										
Na_2CO_3	165	165	167	170	172					
$NaHCO_3$	115	115	115	115	117					
$CaCO_3$	50	77	110	137	162					
MgO	15	30	87	187	305					
Mag. trisilicate	5	7	10	12	15					
$MgCO_3$	5	5	7	7	17					
$BiCO_3$	5	5	5	5	5					
Solutions										
$Al(OH)_3$gel (18·5 ml.)	10	10	12	12	17					
Titralac (7·2 ml.)	167	170	175	177	180					
D.A.S.C. (10·0 ml.)	15	25	25	27	32					
Aludrox (19·5 ml.)	17	27	32	42	62					
Orcine (19·5 ml.)	45	45	47	50	62					
Mucaine (19·5 ml.)	30	30	32	35	50					
Kolantyl gel (16·7 ml.)	57	57	60	62	67					
Milk of magnesia (12·0 ml.)	325	332	332	332	332					
Tablets (1g)										
Gastrogel						1	2	5	7	20
Gastrobrom						5	10	15	20	28
Glysinal						0	0	2	2	5
Actal						7	7	7	7	7
Amphotab						1	2	2	2	5
Gelusil						1	2	2	2	7
Nulacin						2	5	10	15	22
Kolantyl wafer						1	5	5	7	12
Sebella						1	2	2	5	7
Titralac						2	22	42	62	100
Rabro						2	25	32	45	55
Almacarb						1	2	3	4	6
Dijex						3	4	5	6	7

TABLE 3.—AMOUNT OF VARIOUS ANTACIDS REQUIRED TO NEUTRALIZE 50 MEQ HYDROCHLORIC ACID

Antacid	*Neutralizing Capacity of 1 g. or 1 ml.*		*Dose Required to Neutralize 50 mEq. HCl*	*Dose Required in Terms of Drachm Doses*
	ml. N/10 HCl	*mEq. HCl.*		
Powders				
$NaHCO_3$	11.5	11.5	4.4 g.	1.1
MgO	8.5	8.5	5.9 g.	1.5
$CaCO_3$	11.0	11.0	4.5 g.	1.2
Mag. trisilicate	1.0	1.0	50 g.	12.9
$MgCO_3$	0.8	0.8	63 g.	1.6
Solutions				
$Al(OH)_3$ gel	0.7	0.07	715 ml.	201.1
D.A.S.C.	2.6	0.26	192 ml.	54.1
Milk of magnesia	27.7	2.8	17.8 ml.	5.0
Titralac	24	2.4	20.6 ml.	5.9
Aludrox	1.7	0.17	294 ml.	82.8
Oxaine	2.4	0.24	208 ml.	58.6
Mucaine	1.7	0.17	294 ml.	82.8
Kolantyl gel	3.4	0.34	147 ml.	41.4
			Weight of Tablet	*No. of Tablets*
Tablets				
Gastrogel	5.0	0.5	100 g.	1.08	93
Gastrobrom	15.0	1.5	33.3 g.	1.48	23
Glysinal	2.5	0.25	200 g.	0.72	278
Actal	7.7	0.77	65 g.	0.60	109
Amphotab	2.5	0.25	200 g.	1.04	192
Gelusil	2.5	0.25	200 g.	1.36	147
Nulacin	10.0	1.0	50 g.	3.12	17
Kolantyl wafer	5.0	0.5	100 g.	1.64	61
Sebella	2.5	0.25	200 g.	0.53	379
Titralac	42.5	4.25	11.8 g.	0.65	18
Rabro	32.5	3.25	15.4 g.	1.54	10
Almacarb	3.0	0.3	167 g.	1.28	130
Dijex	4.6	0.46	109 g.	1.65	66

further increase gastric secretion, nor is it possible to assess the effects of inadequate mixing of the antacid and its selective discharge from the stomach. Nevertheless, the amount of antacid required in male duodenal ulcer patients, as calculated by the method proposed, corresponds well with the amount of sodium bicarbonate that Price and Sanderson found to be necessary to maintain gastric pH above 4 when this agent was given by continuous intragastric drip.

II. Evaluation of antacids in vitro.—Piper and Barbara H. Fenton[2] titrated known amounts of various antacid preparations to pH 4.5 with N/10 hydrochloric acid at room temperature. When powder was used, the amount tested was 40 mg.; with liquid preparations, 4 ml.; and one whole tablet in the case of tablet preparations. Titrations were carried out im-

(2) Gut 5 585-589, December, 1964

mediately after mixing the antacid in distilled water, and at 5, 10, 30 and 120 minutes after mixing.

The neutralizing capacity of 1 Gm. of various preparations is shown in Table 2. In Table 3 the amount of each acid required to produce a neutralizing capacity of 50 mEq. is given; this is the hourly amount required to provide adequate neutralization in 90% of male duodenal ulcer patients as calculated by the method of Myhill and Piper.

The great variation that exists among commonly used antacids is evident Long-acting antacids have little advantage over rapidly acting preparations, because the half-life of gastric emptying varies from 9 to 30 minutes (mean, 21.8). Each of the more effective antacids—sodium bicarbonate, magnesium oxide or hydroxide and calcium carbonate—has disadvantages in terms of systemic effects or induction of diarrhea or constipation. In the case of less-effective antacids such as aluminum hydroxide gels, the dose required is enormous by comparison with that usually used. Obviously, a standard dose and form of antacid does not exist, and it may be preferable that a combination of antacids should be used with the aim of obtaining maximum antacid and minimum side effects

Since the dose of antacid required is so large as to make neutralization of gastric contents almost impossible, further agents such as anticholinergics should be used. On the other hand, some preparations may act beneficially not only as antacids but as adsorbents that bind pepsin.

The computations of Piper and his associates are an ingenious exploitation of the essentially physiologic data that have been gathered concerning rates of gastric secretion and emptying in man From a practical viewpoint, however, the huge doses which would seem to be necessary to achieve neutralization—some 5 5 l aluminum hydroxide gel per 12 hours in a male duodenal ulcer patient, for example—merely emphasize what we know already, namely that the complete neutralization of gastric acidity is an ideal which can never be achieved in the ordinary day-to-day management of our duodenal ulcer patients Fortunately, most ulcers appear to heal very satisfactorily if gastric acidity is neutralized only part of the time

The Price and Sanderson article cited by Myhill and Piper is abstracted in the 1936-37 Year Book, page 499, and elicited somewhat similar editorial comments as to the large amounts of sodium bicarbonate required to keep gastric pH above 4 At that time, however, I was concerned that partial neutralization though it might heal the ulcer, might not be as beneficial from the standpoint of long range therapy as a dosage schedule aiming at complete neutralization Piper and his associates also assume that complete neutralization is the ideal of ulcer therapy At present I am not so sure Although Piper flatly dismisses the concept of acid rebound, the tremendous amount of

experimental work dealing with the gastric antrum has shown quite conclusively that this organ elaborates gastrin in the presence of neutral gastric contents and does not do so (or perhaps even elaborates an inhibitory agent) when the gastric contents are acid. Total gastric neutralization by antacids would therefore lead to maximal antral stimulation and, theoretically, maximal gastrin production. This, in turn, might enhance gastric acid production not by "acid rebound," but by gradual stimulation of parietal cell function or mass. Seen in this light, total neutralization of gastric acidity by antacid therapy may not only be a goal that is impractical but one that is actually undesirable.

The authors properly point out a number of technical limitations that may affect the significance of their calculations. In particular, the decision to titrate to neutrality imposed a difficult task on the aluminum hydroxide gels which are amphoteric and relatively more effective in bringing the pH of an acid solution to 3.5 than to 7. Perhaps the entire question of the amount of antacid needed to maintain a pH of a certain level in the stomach could be more easily solved by methods that make use of constant recording of intragastric pH. —Ed.]

Treatment of Gastric Ulcer with Carbenoxolone Sodium and Estrogens was re-evaluated by R. Doll, I. D. Hill and C. F. Hutton[3] (Central Middlesex Hosp., London), who in a previous trial had found carbenoxolone to be effective. Carbenoxolone, previously known as Biogastrone, is a pentacyclic triterpene prepared from the liquorice glycoside, glycyrrhizinic acid. It has an anti-inflammatory effect in animals and in some skin diseases and may cause sodium and water retention in some patients. Estrogens were also used in some patients to determine their effect, since they have previously been said to aid the healing of duodenal ulcers.

Patients with well-established radiologic diagnoses of gastric ulcer, more than 10 sq. mm. in area, were divided into four groups. Men under age 60 years received (1) 100 mg. carbenoxolone sodium 3 times a day and 0.5 mg. stilbestrol twice a day; (2) carbenoxolone sodium and dummy tablets in place of stilbestrol; (3) stilbestrol and dummy tablets in place of carbenoxolone; or (4) two sets of dummy tablets. Men over age 60 were treated similarly, except the dose of carbenoxolone sodium was reduced to 75 mg. Women over age 60 were treated like men of the same age, except that 0.5 mg. estriol was substituted for stilbestrol. For women under age 60, both estrogen and corresponding dummy tablets were omitted.

All patients were treated on an ambulatory basis. They took a normal diet, apart from avoiding fried food, ate or drank a glass of milk at least every 3 hours, stopped smoking if possible and used antacid tablets as needed for pain relief. Treatment was continued, in the absence of serious side

(3) Gut 6:19-24, February, 1965

effects, for 4 weeks, and repeat x-ray examination was carried out 1 week later. Neither the physician nor the radiologist knew which treatment had been given individual patients except patients who had obvious side effects.

In both the present and the previous trial, about 40% of the ulcers healed in response to carbenoxolone, but proportionately more ulcers healed in the control series in the second trial (27%) than in the first (5%). The average amount of healing was similar in both trials, 72 and 78% in those receiving carbenoxolone, and 35 and 39% in the controls. The probability of obtaining such differences by chance alone are small. 0.001 in the previous and 0.006 in the present trial. The average number of days required for pain to subside in the present trial was 9 in those receiving carbenoxolone, as opposed to 4.4 in the controls, but the difference was not quite statistically significant ($0.1 > P > 0.05$).

When patients who were given estrogens were grouped together, including those given carbenoxolone sodium and those who were not, average reduction in ulcer size was 73%, as opposed to 57% in the control group. This difference, however, was not statistically significant.

Analysis of the groups revealed that they were quite comparable, although in both trials the patients given carbenoxolone tended to modify their smoking habits more than did the controls. In 5 patients receiving carbenoxolone, edema of the ankles developed, and 4 complained of dyspnea, including 2 of those with edema. All these patients gained weight before onset of these symptoms. Repeated blood pressure measurements were made in only 3 patients. Systolic pressures tended to increase by 20 and diastolic by 12 mm Hg. Some patients had heartburn, and 1 complained of severe chest pain, but the relation of these symptoms to the drug was not clear.

On the whole, the study confirmed the findings of the previous trial that carbenoxolone sodium promotes healing of gastric ulcers. The reason for this beneficial effect is not known.

► As pointed out in the 1963-64 YEAR BOOK, page 523, the authors appeared surprised at the results of their first study indicating that a licorice compound promoted the healing of gastric ulcers (there was no apparent effect in those with duodenal ulcer). They now have double-checked their results and seem ready to accept that carbenoxolone has a place in the treatment of gastric ulcer. One is somewhat concerned, however, that in this series pain tended to last longer in patients receiving carbenoxolone. This is especially

true in view of the fact that antacid tablets were taken "as necessary for the relief of pain," suggesting the carbenoxolone treated patients might have taken more antacids In an otherwise careful evaluation, this factor does not seem to have been controlled A recent study of a limited number of ulcer cases, incidentally, did not find carbenoxolone beneficial (Lancet, I 1030, 1963)

Though perhaps not perfect, double blind therapeutic studies carried out by such people as Doll, Hill and Avery Jones are about as expertly and faithfully performed as is humanly possible The same cannot be said for other "double-blind" studies, for the use of this magic phrase, the random selection of matched patients, and the utmost secrecy about the nature of the medication being taken by a given patient, cannot compensate for studies that are physiologically or clinically nonsensical. There is for example, a report in the *British Medical Journal* (1 753, 1965) of a "Double blind Trial of Bismuth Aluminate and Magnesium Trisilicate in Peptic Ulceration with Simultaneous Gastric Analysis " The results, analyzed by the statistical method of sequential analysis, yielded a clear and statistically significant result in favor of bismuth aluminate with respect to the disappearance of a number of clinical phenomena usually associated with ulcer activity This "significant" difference between the two groups was obtained after the patients "were put on either 1 6 g of magnesium trisilicate before meals for one month or 1 6 g of bismuth aluminate before meals for one month They were given no other treatment They were kept in bed for the first two weeks " The real meaning of the results is unequivocal statistically sound double-blind trials *can* prove that one placebo (or at the best homeopathic) treatment is better than another! Perhaps only the naive are surprised A double-blind study on "The Objective Efficacy of Prayer" came within a one patient breadth of showing that prayer by a group that knew neither patient not physician (or vice versa) was helpful (J Chron Dis 18:367, 1965).

In another article (Am J. Med Sc 247 669, 1964) the results in terms of clinical improvement indicated that patients with hiatal hernia, esophagitis and gastritis fared better if their antacid preparation contained oxethazaine (a local anesthetic) than if it did not One trouble here is that the multiple conditions studied (irrespective of their theoretical need for antacids) included patients with such unusual diagnoses as "achalasia complicated by cardiospasm." Perhaps even more questionable is the validity of a "double blind" study in which one of the agents used had such a striking flavor that 3 patients objected to the taste – Ed]

Ulcerogenic Tumor of Pancreas is reviewed by Robert M. Zollinger and George N. Grant[4] (Ohio State Univ.). In the past 10 years, more than 250 cases of nonbeta islet cell tumors of the pancreas associated with gastric hypersecretion and a high incidence of peptic ulcer have been reported. In addition to this triad, enteritis should be added to the clinical syndrome, this symptom occurring in about 40% of patients, and as the only complaint in 10%. Enteritis may occur because the excessive gastric acid secretion lowers the pH of the duodenal contents sufficiently enough to inhibit the action of pancreatic enzymes, or diarrhea may be the direct effect of the hormone released by the pancreatic tumor. The major symptoms are severe ulcer pain (90%), dehydration

(4) J A M A 190 181 184, Oct 19, 1964

(62%) often associated with hypokalemia, gastrointestinal bleeding (45%), ulcer perforation (44%), and obstructive symptoms related to the ulcer (23%).

The clinical diagnosis may be supported by tests of gastric secretion. About 85% of patients secrete 2,000 cc. or more of gastric juice in a 12-hour overnight test as opposed to the normal figure of 350 cc. In 75%, the concentration of hydrochloric acid exceeds 100 mEq./L. If a maximum histamine stimulation test is performed, acid output is not markedly enhanced since gastric secretory activity is already near maximum Gastrointestinal x-ray examination may reveal an atypically located ulcer in the distal duodenum or upper jejunum The gastric rugae are large and prominent, and the small bowel exhibits a sprucelike pattern and rapid transit time Especially significant is the finding of multiple ulcers, which occur in 12-15% of patients. Involvement of endocrine organs other than the pancreas occurs in about 10%.

Approximately 62% of the tumors are malignant, and metastases are found in two thirds of such cases. Even the benign tumors are multiple in 25% of cases. In other words, more than half the patients have multicentric tumors elaborating the gastric secretory stimulant. Thus, in less than half the cases does removal of a single tumor promise the patient cure, and this fact is a strong argument in favor of total gastrectomy as the treatment of choice. The presence of metastatic lesions does not contraindicate total gastrectomy, for these tumors grow slowly, and prolonged and comfortable survival is possible

Zollinger-Ellison Syndrome: Re-appraisal and Evaluation of 260 Registered Cases by Edwin H. Ellison and Stuart D. Wilson [1] yielded the following statistics. Of the patients, 144 (57%) died, usually as a result of severe ulcer disease. The sex incidence was 6 males to 4 females, and the age at onset of symptoms was predominantly in the 3d to 5th decades. Twelve patients, however, were under age 15. Operation was performed on 230 patients (88%) Chronic pain characterized 69% of the patients, gastrointestinal bleeding 45% and symptoms produced by fluid loss 62%. Diarrhea alone was noted in 17 (7%) In 8, the serum potassium was less than 1.9 mEq L. The location of the primary ulcer is shown in Figure 52 Although many of the ulcers were atypically located, it

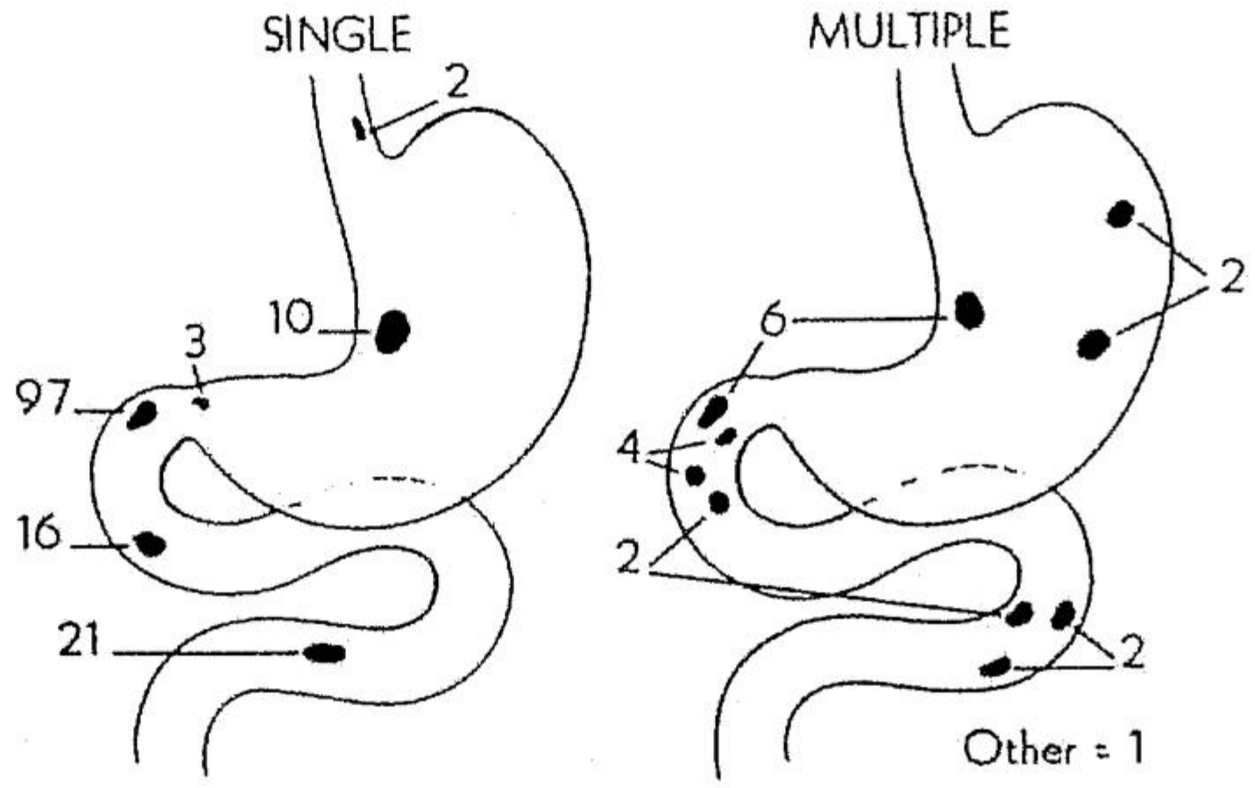


Fig. 32.—Note that 74% of the primary ulcerations occurred at the usual site of the average duodenal ulcer. In addition, gastric ulcer occurred in only 18 patients and 6 of these had an associated duodenal ulcer. (Courtesy of Ellison, E. H., and Wilson, S. D.: Ann. Surg. 160: 512-530, September, 1964.)

should be emphasized that three fourths of the ulcers occurred in usual locations.

Fifty-six patients (21%) had evidence of an associated endocrine disorder, but in only 8 (3%) was there multiple endocrine involvement. Half of the 56 had a parathyroid adenoma and 17 a pituitary tumor. A familial incidence of peptic ulceration was reported in 22 (8%).

In 155 (94%) of 164 patients who had an adequate secretory study, hyperacidity was present. Seven (4.5%) had hypoacidity and achlorhydria. In 47 (85%) of 55 patients studied, the volume of secretion was over 1,000 ml. in a 12-hour overnight test; in 40 of 54, gastric hydrochloric acid concentration exceeded 100 mEq./L.

Eighteen of 39 patients whose initial surgical procedure included resection of the tumor are living. Subtotal gastrectomy as well as tumor resection was carried out in 75 patients, with an over-all survival of 39 (52%). The best results occurred in 22 patients who had total gastrectomy with or without resection of tumor. Nineteen of these are living. This figure includes those who had total gastrectomy as a second or a third operation; in 10 patients who had total gastrectomy as their first definitive ulcer procedure, survival was 100%. Total gastrectomy therefore is the operation of choice but is not advisable without a definitive tissue diagnosis.

Three fifths of the tumors are malignant, and 44% of the total number of patients had metastatic lesions when first diagnosed. Ten per cent had diffuse hyperplasia or microadenomatosis. Positive lymph nodes were found in 80 patients (53%) with malignant disease, and 48% showed lesions in the liver. The lungs were only involved twice.

► [When this volume of the YEAR BOOK is published, the Zollinger-Ellison syndrome will be celebrating its 10th birthday It thus is most appropriate to abstract reviews of this syndrome by its two fathers Little can be said about these excellent summaries, although Doctor Ellison obviously has not been told about some of the patients who died of postoperative complications when total gastrectomy was carried out as an initial procedure Perhaps for fear of such accidents, or because of the morbidity which follows total removal of stomach, others recommend a more conservative approach, with emphasis on excisional tumor therapy (Am J Surg 108 132, 1964)

Perhaps the most interesting theoretical problems pertaining to the Zollinger Ellison syndrome are (1) its relation to tumors of other endocrines and (2) the question of whether or not patients with diarrhea and gastric hypoacidity should really be classified as examples of the Z-E syndrome Thus, a call for a "reappraisal" is sounded by Huizenga, Goodrick and Summerskill (Am J. Med 37 564, 1964) These authors contend, "In the majority of instances the Zollinger Ellison syndrome represents the gastrin-secreting islet cell tumor component of familial polyglandular endocrinopathy" The following article presents the same viewpoint

As usual, it is a matter of definition To me, the typical Zollinger-Ellison syndrome, characterized by fantastic gastric hypersecretion, a tumor originating in the pancreas, severe acid peptic disease, and often by diarrhea, should stand by itself It can well be separated from the polyglandular syndrome or a parathyroid adenoma with ulcer in most cases, and it is quite distinct from the syndrome of peptic ulcer associated with hypoglycemia producing beta cell tumors of the Islands of Langerhans In addition, it would seem particularly important to exclude from the Zollinger Ellison syndrome patients without gastric hypersecretion and ulcer forming tendency The nature of the responsible tumors in theses cases is far from clear and as is apparent in the article by Melmon presented in this YEAR BOOK that tumors of this type are sometimes included in the spectrum of carcinoid disease According to expert pathologists, indeed, the histologic differentiation of certain carcinoids from non beta cell tumors of the Islands of Langerhans may be exceedingly difficult if not impossible – Ed]

Familial Multiple Endocrine Adenoma-Peptic Ulcer Complex. Harold S. Ballard, Boy Frame and Robert J. Hartsock[6] report on 11 cases occurring in a single family and review 74 others reported in the literature. The first family was described by Rossier in 1939: Two sisters had pluriglandular disease, and the male members of the sibship had peptic ulcer without apparent endocrine involvement. Analysis of all 85 cases showed that both sexes and all ages were affected without any particular preponderance of incidence. The most common presenting clinical features were symptoms of peptic ulceration, found in 21 cases. Altered parathy-

COMBINATION OF TUMOR, TUMORS OR ADENOMATOUS HYPERPLASIA AND PEPTIC ULCERATION IN 49 OF 85 CASES

COMBINATION	CASES	
	No.	%
Parathyroids, pancreas, pituitary, peptic ulceration	22	45.0
Parathyroids, pituitary, peptic ulceration	2	4.0
Pituitary, pancreas, peptic ulceration	6	12.2
Parathyroids, pancreas, peptic ulceration	14	28.5
Adrenals, parathyroids, ulcer	1	2.0
Parathyroids, pancreas (?) ulcer	4	8.0

roid function marked onset in 8. In 3, severe diarrhea and weight loss were the prominent initial manifestations.

Evidence for hyperfunctioning parathyroid glands was present in 74 of the 85 cases, and in 39 (53%), the hyperplasia or tumors of the parathyroid were multiple, thus differing in this regard from the usual finding in primary hyperparathyroidism. However, conspicious clinical manifestations of renal and skeletal disease were lacking. Pituitary lesions were described in 55 cases, with symptoms chiefly those of the mechanical effects of an intrasellar mass. Acromegaly was present in 15 cases. The pancreas exhibited tumors in 69 cases, the incidence of beta and nonbeta cell tumors being about evenly divided.

Peptic ulcer occurred in 49 patients (table) and was associated with pancreatic tumor or clinical hypoglycemia in 43. Gastric hypersecretion was documented in 15 patients. Diarrhea occurred in 11 patients, the stools being typically watery and not offensive. Four patients had documented steatorrhea. While a positive endocrine influence underlying peptic ulceration in the familial multiple endocrine adenoma complex is not proved, it is reasonable to believe that some of the tumors secrete gastrin or gastrin-like material. The role of parathyroid overactivity in causing peptic ulceration is debated. If there is an increased tendency toward peptic ulcer and hyperparathyroidism, the mechanism is unknown; there is no evidence of increased acid secretion because of parathyroid overactivity.

Study of the genetic aspects of the syndrome showed that (1) every affected person had an affected parent; (2) affected persons married to normal persons had, on the average, affected and normal offspring in equal proportions; and (3)

normal children of affected persons, when they in turn married normal persons, had only normal offspring. Thus, the multiple endocrine adenomatosis-peptic ulcer complex shows the pedigree characteristics of autosomal dominant inheritance.

In support of these generalizations, the authors present 6 generations of a family comprising 42 members. Of these, 16 were affected or probably affected, and 11 of the 16 had an ulcer diathesis.

Gastroduodenal Channel after Pyloroplasty and Vagotomy: A Cineradiographic Study was performed by Claude Bloch and Bernard S. Wolf[7] (Mount Sinai Hosp., New York) on 21 patients, all of whom had had a Heineke-Mikulicz pyloroplasty for chronic duodenal ulcer. This consisted of a longitudinal incision about 4 in. long, 2 in. on either side of the pyloric ring, which was closed in a vertical fashion. All patients had concurrent transabdominal vagotomy. Studies were carried out principally 3-10 weeks after operation.

After pyloroplasty, normal landmarks are no longer identifiable. The gastroduodenal channel apparent postoperatively represents that portion of the lumen of the gastric antrum and of the proximal part of the duodenal bulb through which the pyloroplasty incision has been made. The ridges which outline the contours of the gastroduodenal channel are produced by the divided pyloric muscle ring and by the vertical

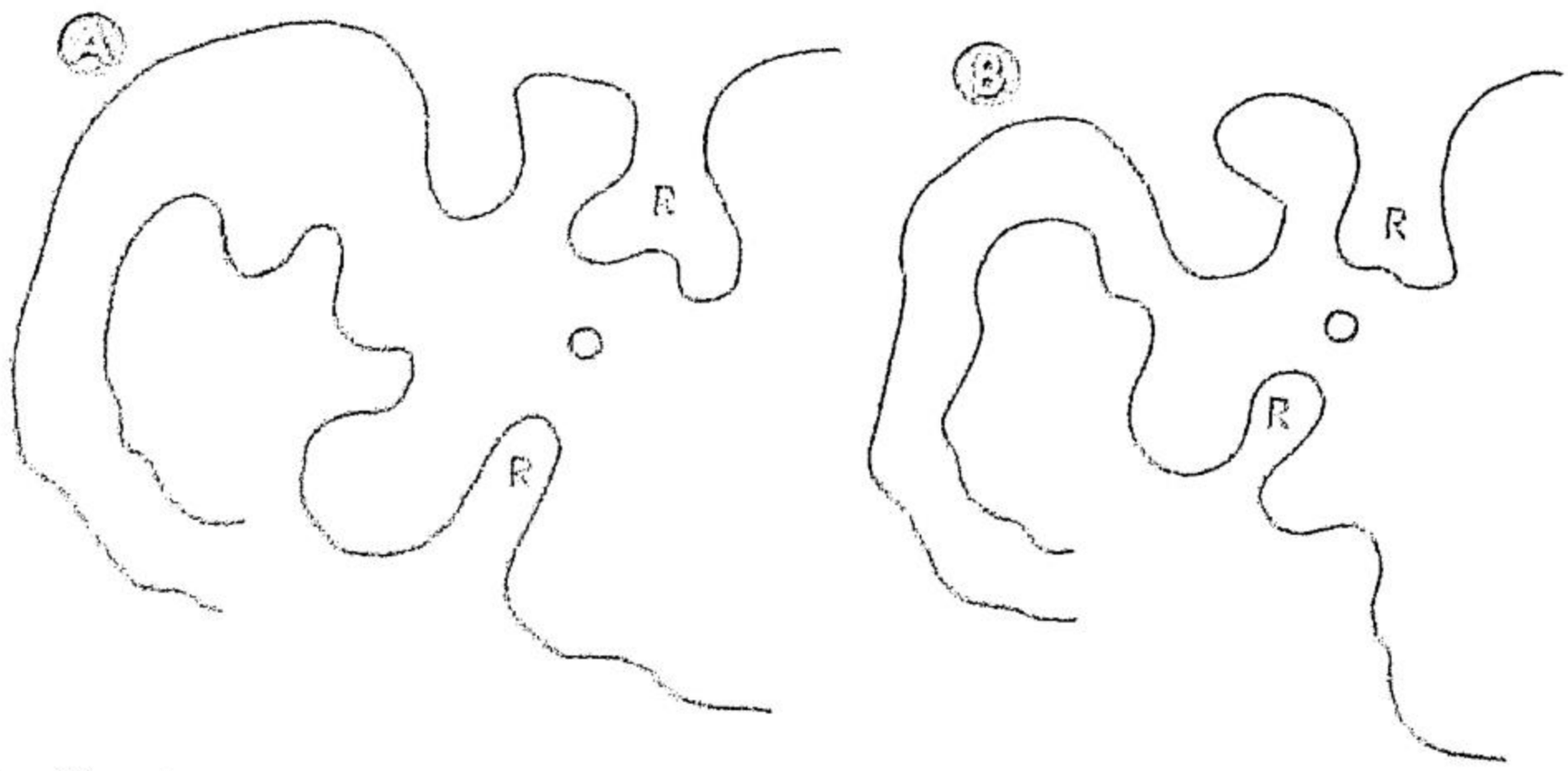


Fig. 52.—Outline drawings from cine frames of typical postoperative appearances. A, the gastroduodenal channel (O) is broad and gaping, and its caliber is defined by elongated ridges (R). Inflow pseudodiverticula are noted along both curvatures just distal to the ridges. B, the gastroduodenal channel (O) has remained unchanged in caliber, and the ridges (R) have maintained the same configuration and size; the pseudodiverticula are slightly smaller than before. (Courtesy of Bloch, C., and Wolf, B. S.: Radiology 64:43-51, January, 1955.)

closure of the pyloroplasty incision. Pseudodiverticula are characteristically observed just distal to these ridges and are puckerings of the wall caused by the nature of the closure (Fig 53).

In 11 of the 21 cases, a configuration considered typical of a successful pyloroplasty was seen. The gastroduodenal channel was broad, patulous and asphincteric. Its contours were defined by ridges which changed little during phases of filling or emptying. The distal wall of the ridges corresponded to the proximal border of the pseudodiverticula. The latter varied in size and shape but typically had long narrow necks and axes perpendicular to the lumen of the gastroduodenal channel. During filling and emptying, these pseudodiverticula occasionally changed markedly in size and shape (Fig 53). In the patients showing the typical postoperative findings, there was no delay in passage of the barium suspension or of a 12.5-mm. barium pill through the gaping gastroduodenal channel.

In 4 of the 21 cases, the pyloric channel was narrow, and the typical ridges and pseudodiverticula were not seen. These were considered to be unsuccessful pyloroplasties, although none of the patients had any signs of gastric retention of the liquid contrast meal. A barium pill, however, passed through the channel with difficulty. In the remaining 6 cases, an intermediate situation was seen in that some but not all the characteristics of the successful pyloroplasty were evident.

Although many of these features may be discerned on the basis of routine gastrointestinal x-ray examination, cinera-diographic examination permits better evaluation of the distensibility and the patulous character of the gastroduodenal channel after pyloroplasty, and the varying filling of pseudodiverticula is helpful in differentiating such pockets from possible recurrent ulcerations.

► In view of the increasing popularity of performing some sort of drainage procedure in the surgical treatment of duodenal ulcer, these are bound to be valuable studies One wishes, however, that the authors had pursued the subject in greater depth and had avoided language which, though conventional for the radiologist, is not clear to the average reader Thus, one has to assume that "horizontal" and "vertical" when used in referring to the pyloroplasty procedure are intended to mean "axial" and "transverse," respectively, with the gut lumen as the point of reference It is also not clear to what extent preoperative duodenal deformities (which also may show what might be interpreted as "ridges" and pseudodiverticula) contribute to the postoperative findings Pathologic evidence would have helped to establish the identity of

the ridges and the cut pyloric musculature As it stands, the one critical finding is the patulous gastroduodenal channel and this one criterion, it would seem, is the hallmark of the successful pyloroplasty – Ed.]

Clinical Significance of Nonspecific Gastritis is viewed with considerable misgivings by Eddy D. Palmer[8] (Brooke Gen'l Hosp.). The results of postmortem examinations, of endoscopic observation and of histopathologic studies of biopsy specimens have all led to one-sided views, and the recent emphasis on such pathologic studies has been responsible for totally morphologic concepts to the exclusion of clinical evaluation. The most important fact revealed by gastric biopsies is that the gastric mucosal response to injury is nonspecific. If rare specific forms such as syphilitic, tuberculous and sarcoid gastritis are excluded, only one type of chronic gastritis remains; this is nonspecific gastritis, manifested in a series of progressive stages.

Although many clinical phenomena have been blamed on gastritis, the link between gastric mucosal abnormality and the patient's symptoms has not been made clear to date. Gastritis, indeed, remains a diagnostic excuse more than anything else There is no reason to believe that inflammation of the gastric mucosa can cause gas, cramps, pains, nausea, anorexia and all other forms of dyspepsia. On the other hand, the complications of gastritis may have a serious outcome. Loss of acid, pepsin and intrinsic factor may impair digestion and nutrition In addition, there is some evidence that gastritis is a precursor of neoplasia. At present, however, the most important complication of gastritis is hemorrhage, a complication which may affect gastritis at any of its stages.

[When Eddy Palmer writes, "I believe that uncomplicated chronic nonspecific gastritis causes no illness For many decades a concept of gastritis has been used as a diagnostic 'excuse' to cover dyspeptic symptoms that have not been understood," I could stand up and cheer Since there are no characteristic diagnostic features of gastritis, since it produces no recognizable uniform symptom complex (except in its most advanced atrophic forms) and since there is no generally accepted form of therapy, it has always impressed me as a vague entity which should not be included in the diagnostic armamentarium except under the most specific circumstances Perhaps Palmer and I are both skeptical curmudgeons, but there is no important difference between us: he is an expert in gastroscopy and gastric pathology, and I am a duffer in these skills The duffer can now advance with more confidence under the banner of the expert – Ed.]

Recovery of Gastric Mucosal Structure and Function in Pernicious Anemia during Prednisolone Therapy is reported in a case studied by Graham H. Jeffries.[9] (Cornell Univ.).

[8] Am J Digest Dis 10:44-97 January, 1965
[9] Gastroenterology 48:271-278 March, 1965

Woman, 75, was diagnosed in 1962 as having pernicious anemia on the basis of a macrocytic anemia with a hemoglobin of 7.2 Gm /100 ml , leukopenia, megaloblastic bone marrow, 0 excretion of vitamin B_{12} on a Schilling test and neither free acid on histamine stimulation nor intrinsic factor in the gastric juice She responded to parenteral vitamin B_{12} injections with a reticulocytosis of 19%

In 1964, hematologic studies yielded normal results Gastric acid was still absent on histamine stimulation, and no intrinsic factor was found in gastric juice Gastric mucosal biopsy showed atrophy with mononuclear infiltration Parietal cells were not found in 4 specimens, but a few were identified in a fifth specimen Two Schilling tests again revealed very low urinary excretion of vitamin B_{12}. The patient's serum contained antibodies to intrinsic factor and to parietal cells

Prednisolone, 20 mg daily, was given orally for 4 months. Toward the end of this time, gastric secretion, both fasting and stimulated, contained free hydrochloric acid, with a pH as low as 2.0; it also contained intrinsic factor The Schilling test showed that 21% of the radioactive test dose of vitamin B_{12} was excreted in the urine In addition, when 10 ml. of the patient's stimulated gastric juice was given with radioactive B_{12} to another patient with pernicious anemia, normal vitamin B_{12} to another patient with pernicious anemia, normal vitamin B_{12} absorption took place. Four gastric mucosal biopsy specimens showed normal gastric glands containing abundant parietal and chief cells in all specimens The titer of intrinsic factor antibody in the patient's serum decreased, but parietal cell antibody titer did not change.

One theory holds that autoimmune mechanisms either initiate or perpetuate the gastric mucosal lesion in the pernicious anemia. The effect of glucocorticoids on the gastric mucosa of this patient is thus of particular interest, for prolonged suppression of the postulated immunologic process by prednisolone may have permitted regeneration of gastric glands with restoration of acid and intrinsic factor secretion. If this was the case, the improvement in gastric mucosa in the absence of a change in titer of circulating parietal cell antibody suggests that this antibody and mucosal cell damage may not be causally related.

► [In 1960, Kristensen and Friis reported that steroids increased intrinsic factor secretion and vitamin B_{12} absorption in patients with pernicious anemia (Acta med scandinav 166:249 and 168 457, 1960). The article here abstracted supports these findings in a dramatic manner. It should be noted that some parietal cells were found in the patient's gastric mucosa 2 years after the diagnosis of pernicious anemia was made, and before she had prednisolone treatment. According to traditional concepts of pernicious anemia, no parietal cells whatsoever should characterize the real disease.

A good summary of the current status of gastric atrophy with respect to secretion of intrinsic factor has been written by George B Jerzy Glass (Am J Digest Dis. 10 376, 1965).—Ed.]

Survey of Food Intolerances in Hospitalized Patients was

carried out by James P. Koch and Robert M. Donaldson, Jr.[1] (Boston VA Hosp.) to test the belief that the ingestion of certain foods initiates or aggravates various gastrointestinal symptoms One of the authors interviewed the patients without being aware of their diagnoses and asked them standard questions to determine whether any food or foods caused symptoms such as heartburn, belching, nausea, vomiting, aftertaste, epigastric pain, abdominal pain, bloating, flatulence, diarrhea or constipation. The second author, who did not know the results of the interview, classified the patients according to clinical criteria. The patients were drawn from the general medical ward, the gastrointestinal unit, and the x-ray department and consisted of consecutive admissions or referrals, only those unable to answer easily and consistently being eliminated.

Of the 655 patients studied, 570 incriminated one or more foods as a cause of gastrointestinal symptoms. Six of the foods bothered more than 25% of the patients interviewed. The eight most common foods incriminated and the incidence of this incrimination by patients with organic gastrointestinal disorders, with functional gastrointestinal disorders and without gastrointestinal symptoms is shown in the table This table also shows that patients with gastrointestinal symptoms, whether organic or functional, claimed

INCIDENCE OF FOOD INTOLERANCES AMONG 655 HOSPITALIZED PATIENTS (PATIENTS ATTRIBUTING SYMPTOMS TO SPECIFIC FOODS)

Food	Group 1 (390 Patients with Documented Gastrointestinal Disease)	Group 2 (120 Patients with Gastrointestinal Symptoms with No Disease)	Group 3 (145 Patients without Gastrointestinal Symptoms & Disease)	Significance of Difference Group 1 vs. Group 2 (p Value)	Significance of Difference Group 1 + 2 vs. Group 3 (p Value)
	%	%	%		
Cabbage	43.6	40.0	37.9	>0.5	>0.3
Baked beans	34.5	40.2	23.4	<0.01	<0.01
Spicy foods	56.3	30.3	16.6	>0.5	<0.001
Fried foods	33.5	41.7	20.7	>0.1	<0.001
Onions	29.4	35.0	18.6	>0.2	<0.01
Fatty foods	30.4	30.8	15.2	>0.9	<0.001
Orange juice	15.5	19.2	9.7	>0.5	<0.02
Coffee	12.5	17.5	9.7	1.0	<0.02

1. New England J. Med. 271:497-503, Sept. 28, 1964

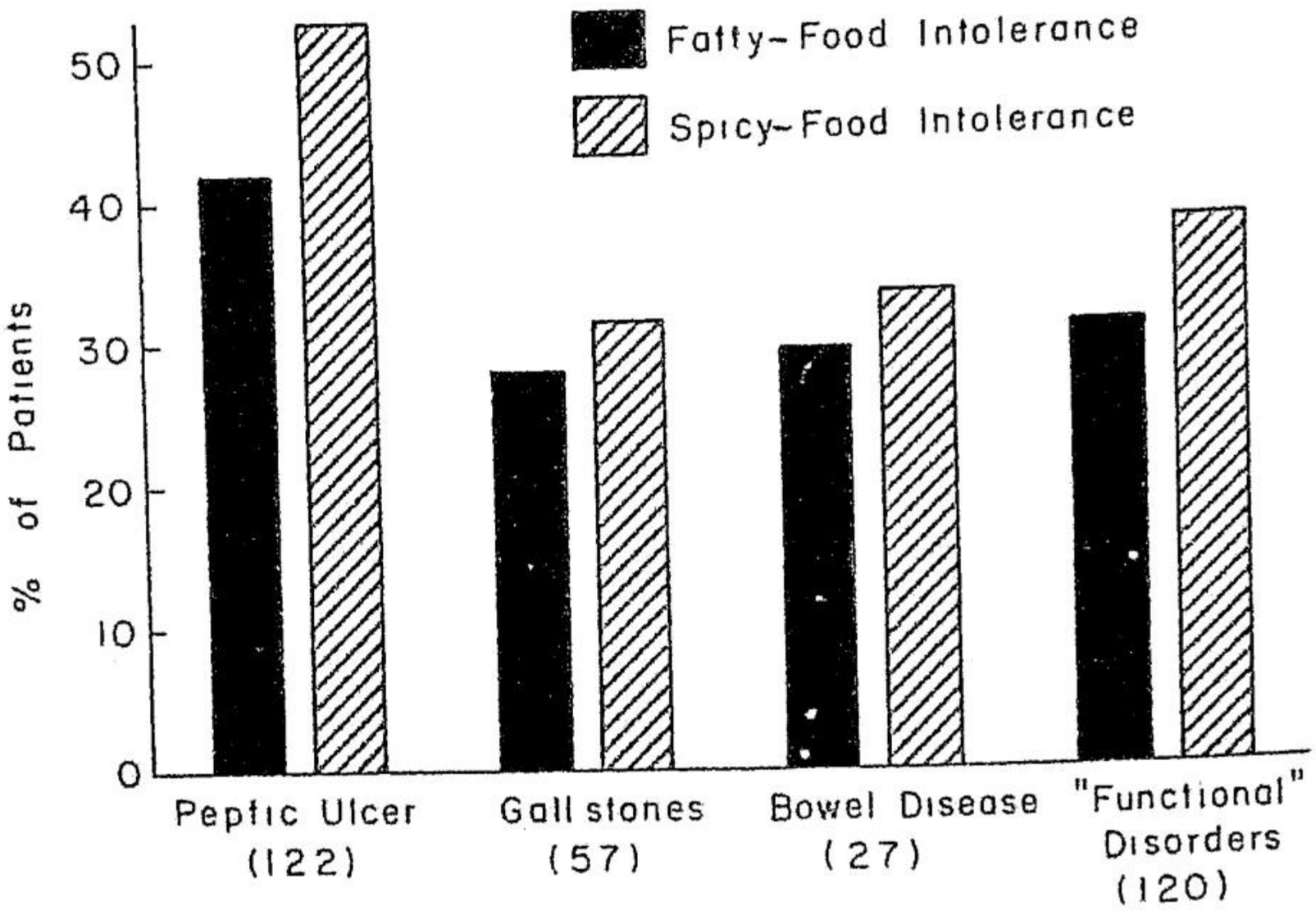


Fig. 54.—Incidence of intolerance to fatty and spicy foods in various gastrointestinal disorders. (Courtesy of Koch, J. P., and Donaldson, R. M., Jr.: New England J. Med. 271: 657-660, Sept. 24, 1964.)

intolerance for each of the foods (except cabbage) significantly more often than patients with no gastrointestinal symptoms. There was, however, no difference in the incidence of various food intolerances between those with documented gastrointestinal disease and those with symptoms but without demonstrable organic changes.

The data failed to show that patients with specific gastrointestinal disorders had any characteristic patterns of food intolerance, and patients with specific gastrointestinal disorders could not be distinguished on the basis of food intolerance. Particularly interesting was the fact that a significant tendency to incriminate fried or fatty foods was not noted among patients with documented gallstones, nor did intolerance to spicy food appear different in patients with peptic ulcer and those with no x-ray evidence of ulcer (Fig. 54).

In general, individual foods did not produce characteristic symptom patterns. A given food was usually blamed for different symptoms by different patients. Constipation, for example, was attributed to milk as often as diarrhea. If a patient was bothered by several different foods, he tended to attribute the same symptoms to each food. Thus, the kind of symptoms attributed to the ingestion of specific foods tended to be characteristic of the patient rather than of the food. Exceptions to this generalization were as follows: most pa-

tients bothered by baked beans complained of flatulence, constipation was frequently attributed to cheese and an unpleasant aftertaste was said to be common after eating cabbage or onions. In addition, 9 of 29 patients with gastrectomy claimed intolerance to milk, 8 of these stating that milk caused nausea or vomiting.

▻ [The task of distinguishing foods that really cause symptoms and disease from those that are believed to cause symptoms and disease is becoming increasingly difficult As this well-planned study shows, many common alleged food intolerances are probably attributable to traditional teaching and beliefs, to the taste and consistency of certain foods, or to other factors which have no rational basis Yet we now accept that the ingestion of gluten may have serious consequences to the patient with nontropical sprue, that disaccharides may produce severe symptoms in certain patients with intestinal enzymatic abnormalities and that the ingestion of certain agents such as galactose and phenylalanine may have fatal consequences in a few It is noteworthy, however, that in these relatively uncommon diseases characterized by real and specific food intolerances, the nature of the offending food has rarely been identified by either patient or physician on the basis of the patient's story that a certain food caused gastrointestinal symptoms – Ed]

Absorption of Alcohol after Gastrectomy. Ronald G. Elmslie, R. A. Davis, Donal F Magee and Thomas T. White[2] (Univ of Washington) studied four groups of subjects: 5 normal controls, 5 patients who had undergone Billroth I gastrectomy, 5 who had undergone Billroth II gastrectomy and 5 who had undergone gastrectomy or pyloroplasty with vagotomy. Each subject was given 1 ml. of 86% proof whisky per kg. body weight after an overnight fast, and the blood alcohol level was determined at 10 minute intervals for 1 hour The difference in results between the normal subjects and gastrectomized patients is shown in Figure 55. Noteworthy were the peak levels in the gastrectomized patients at 20-30 minutes, at which time normal values were only a third as high and still rising progressively. Patients in the miscellaneous group with vagotomy had variable results.

Three-day fat-balance tests showed that normal subjects absorbed more than 97% of the daily intake of 80 Gm. In the other groups, absorbed fat varied between 78% and 97%, but no correlation was detected between fat absorption and the pattern of blood alcohol levels after administration of whisky. Although most gastrectomized patients showed x-ray evidence of accelerated gastric emptying, none had marked dumping symptoms Such mild dumping symptoms as were present could not be correlated with the results of the alcohol tolerance tests.

[2] Surg., Gynec. & Obst. 119 1255-1259, December, 1964

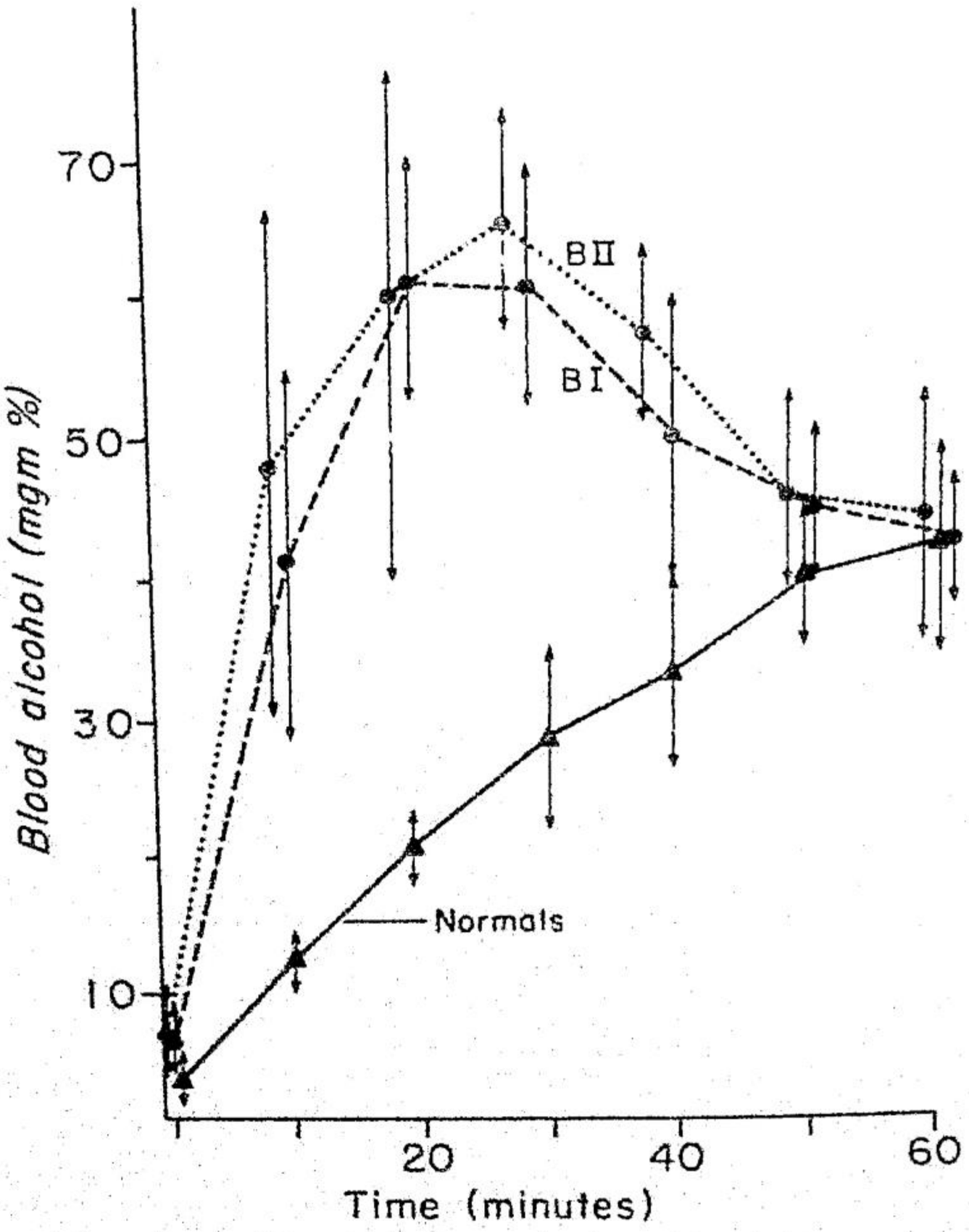


Fig. 55 – Response of normal persons and Billroth I and Billroth II patients to administration of 1 mL whiskey per kg body weight. Double arrows indicate standard deviations. (Courtesy of Elnishie, R. G., *et al.* Surg., Gynec. & Obst. 119:1256-1258, December, 1964.)

Alcohol is a unique carbohydrate because it is absorbed unchanged from all mucous surfaces. In addition, there is no upper limit to the rate of absorption from the small intestine. Since it is unlikely that gastrectomy changes the rate of utilization of alcohol, the results of this study are best explained by rapid entry of the alcohol into the small bowel of gastrectomized patients, with more rapid absorption from this area. Thus it is possible that gastrectomized patients may become legally intoxicated by a dose of alcohol well tolerated before operation.

► [This report seems to substantiate the dictum of one of my more cynical colleagues to the effect that the down-and-out alcoholic who has a duodenal ulcer certainly deserves surgical treatment, not only for relief of the ulcer but because his needs can thereafter be satisfied at half the cost –Ed.]

Dumping Syndrome: IV. Relationship between Substance P and Motility of the Small Intestine, with Special Reference to the Dumping Syndrome. When patients who have had

partial gastrectomy experience the dumping syndrome, the motility of the small intestine is usually increased. Because of this increased motility, it has been postulated that a humoral agent, such as 5-hydroxytryptamine, is released and accounts for some of the clinical manifestations of the syndrome. Another constituent of the intestinal wall with potent motility-stimulating properties is substance P. To determine whether this agent might play a role in the dumping syndrome, Bengt Pernow and Sten Wallensten[3] (Stockholm) analyzed substance P concentration of small bowel tissue that had been stimulated either mechanically or by application of a hyperosmotic solution.

In 19 patients undergoing abdominal surgery related to duodenal ulcer and its complications, a section of intestine was pinched with a pair of tweezers and a specimen of intestinal tissue about 20 mm. long was taken from the irritated area. The defect was then sutured, 50% glucose solution was injected, and after 4-5 minutes, another sample of jejunum of equal size was excised from an adjacent area.

After mechanical irritation of the intestine, motility remained essentially normal, and the concentration of substance P per gram of tissue ranged from 1.3 to 33 units. After glucose solution, intestinal motility responded variably, but in 5 patients the intestine reacted with lively peristalsis. In these 5, intestinal content of substance P increased over that found in the preglucose intestinal sample. In patients with moderately active motility after application of hypertonic glucose, substance P increased slightly, and in those with no change in motility, the mural content of substance P did not increase. In 9 other patients serving as controls, the substance P content of the intestinal wall was analyzed before and after mechanical stimulation alone. Moderate increases in substance P content were found 5 times, usually corresponding with increased poststimulation motility.

Similar experiments were carried out in 4 dogs. In the 2 that responded with lively motility to injection of glucose, the intestinal content of substance P increased, but it remained unchanged in the 2 that did not respond. In 2 other dogs, the intestine was denervated; in these, neither motility nor substance P content changed in response to hypertonic glucose injection.

(3) Acta physiol. scandinav. 120:530-540, November, 1964

Of the 19 patients tested with hypertonic glucose, 9 were undergoing surgery in an effort to correct a severe dumping syndrome after a Billroth II anastomosis. In 6 of these 9, the content of substance P in the gut wall increased after glucose injection In 8 patients operated on for other reasons, increased substance P content after glucose injection was found in only 2.

The results indicate that a correlation exists between the postgastrectomy dumping syndrome and increase in substance P content of the intestinal wall in response to administration of hypertonic glucose, and it is reasonable to postulate that accelerated formation of substance P also results whenever hypertonic material is ingested by subjects who have dumping symptoms.

► [This study is more provocative than convincing It draws our attention, however, to substance P, one of the many enteroactive agents that apparently can affect the motility of the gut Others are serotonin (see the following article and the one by Melmow, also in this chapter), gastrin when used in large doses (see the article by Gregory *et al.* p 357), and acidic lipids such as Darmstoff, etc (see the article by Gray, p. 382) That such substances may be extracted from tissue and that they are enteroactive seem evident beyond question The extent to which they function under normal and abnormal conditions in intact man is, however, unclear at present Whatever their role, it would appear that cholinergic and adrenergic stimuli are but some of the mechanisms that control intestinal function – Ed]

Observations on Significance of 5-Hydroxytryptamine in Relation to Peristaltic Reflex of the Rat. To test the hypothesis that 5-hydroxytryptamine is essential for initiating the peristaltic reflex, D. J. Boullin[4] (Queen's College, Dundee) used both in vivo and in vitro methods to compare intestinal motor function in normal rats, in rats receiving a synthetic diet free of tryptophan and in control pair-fed litter mates receiving the same diet but with added L-tryptophan. In the tryptophan-deficient rats, the 5-hydroxytryptamine content of the small intestine mucosa was reduced by a mean value of 89% as compared with control values. In some of the experimental animals, no mucosal 5-hydroxytryptamine could be detected.

Peristalsis of segments of rat intestine in vitro were studied by (1) recording longitudinal contractions, (2) measuring intraluminal pressure and, in particular, the threshold pressure necessary to initiate the peristaltic reflex and (3) measuring the volume expelled by the segment. Peristaltic re-

(4) Brit J. Pharmacol 23 14-33, August, 1964

sponses and propulsive efficiency in the tryptophan-deficient rats, including 2 in which no mucosal 5-hydroxytryptamine could be detected, did not differ qualitatively or quantitatively from those of control or normal rats.

In control groups, low intraluminal concentrations of 5-hydroxytryptamine (up to 10 μg./ml.) first stimulated and then inhibited peristalsis, higher concentrations inhibited or abolished the reflex, often without prior stimulation. The most obvious effect of 5-hydroxytryptamine was increase in inherent tone of longitudinal muscle. 5-Hydroxytryptamine applied serosally always produced initial brief stimulation with a large single contraction of longitudinal muscle. The effects of 5-hydroxytryptophan applied intraluminally or serosally were qualitatively the same as those obtained by 5-hydroxytryptamine except that much larger amounts had to be used. In tryptophan-deficient preparations, response to applications of 5-hydroxytryptamine or 5-hydroxytryptophan were remarkably similar to those obtained in control preparations except that inhibitory effects of these agents seemed somewhat more marked.

Peristalsis in situ was studied by perfusing isolated portions of rat gut through a cannula inserted into the stomach or the upper duodenum. In studies using the gastric infusion, pyloric function was crucial in that it regulated flow of fluid into the duodenum and thus initiated a duodenal peristaltic response When over-all transport rates were compared in the groups of rats studied, there was no qualitative or quantitative difference between control and experimental animals under basal conditions or after addition of 5-hydroxytryptamine In the case of rat intestine perfused intraduodenally, perstalsis in both tryptophan-deficient and control rats was not easily elicited, and fluid flowed through the gut in more or less continuous fashion. The effect of intraluminal 5-hydroxytryptamine in the experimental animals produced variable results, ranging from inhibition to, in 1 case, marked stimulation of motor activity.

These experiments strongly suggest that 5-hydroxytryptamine is not obligatory as a sensory stimulant or essential for peristalsis in any way. However, the typical transient stimulation of peristalsis by 5-hydroxytryptamine, followed by inhibition, has been described in both man and experimental

animals. Thus the amine may have an ancillary effect on motor function even though it does not exercise an intrinsically essential neurosecretory function.

Effect of Drugs on Intestinal Release of Stimulant Acidic Lipids in Relation to Simultaneous Drug Effect on Intestinal Mechanical Activity In Vitro. Certain acidic lipids derived from body tissues exhibit potent biologic activity on smooth muscle. Among such stimulant lipids are Darmstoff, urin, prostaglandin, menstrual fluid lipids and brain acid. Because the precise physiologic role of these substances is not clear, Grace W. Gray[5] (Marquette Univ.) used bioassays to test (1) effect of drugs on release of acidic lipids by the intestine and (2) effect of the acidic lipids on motor response to drugs by isolated jejunal strips in a smooth muscle bath.

Biodialysate extracts of the acidic lipids were obtained by incubating rabbit small intestine in Tyrode solution containing either no drug or one of the drugs being tested. The material in the biodialysate was extracted, concentrated and then semipurified by a number of procedures, eventually yielding a pale yellow, noncrystalline material. When this material was redissolved, its motility-stimulating effect could always be demonstrated on fresh rabbit jejunal strips, and this effect was not blocked by atropine, hexamethonium, tripelennamine or a serotonin antagonist, nor was it due to presence of potassium in the extracts

Dibucaine hydrochloride, a local anesthetic, did not affect release of stimulant lipid from the intestine, but it blocked motor responses to stimulant lipid extracts at concentrations which did not abolish spontaneous contractile activity. Magnesium chloride, which inhibits motor activity, did not significantly decrease the stimulant properties of the acidic extracts from intestine bathed in Tyrode solution containing this agent. This suggested that release of the stimulant lipid was not merely the result of mechanical activity of tissues.

Epinephrine inhibited spontaneous mechanical activity of the muscle strips, but the period of inhibition was followed by spontaneous recovery of motor activity even during continued drug exposure. The lipid extracts antagonized the epinephrine effects strikingly in that they hastened return of contractile activity and increased contractile amplitude and

(5) J Pharmacol & Exper Therap 146 215-224, November, 1964

tone. The biodialysate extracts from intestine bathed in epinephrine released a material with moderately decreased stimulant activity. These results suggest that stimulant lipids are involved in the mechanism of recovery from epinephrine-induced inhibition of intestinal motility in vitro, and thus may be involved in the mechanism of inhibition itself.

Methoxamine produced effects qualitatively similar to those of epinephrine but not so marked. N-Isopropylmethoxamine, reported to block the metabolic responses to catecholamines, resembled dibucaine in that it had no effect on release of stimulant lipid from the intestine but was effective in blocking motor responses to the extract.

Cholinergic drugs, such as acetylcholine, did not affect release of stimulant lipid from the intestine, but reserpine greatly reduced this release. On the other hand, the lipid extracts did not change the usual motor response to reserpine, which consisted of complete inhibition of spontaneous activity of the muscle strips, and little or no recovery occurred during continued drug exposure.

Although the in vivo role of the extracted stimulant lipid substances is uncertain (they may even be artifacts of extraction), considerable interrelation between drugs, gut motility and the diffusible, lipid-soluble, stimulant substances was demonstrated. It is suggested that the stimulant lipids may act on a neuronal mechanism, perhaps by affecting excitable membrane. In addition, the rhythmicity of the intestine in vitro may be related to a cycle in which functionally important labile acidic lipids are bound and unbound by labile catecholamines

Basic Electric Rhythm of the Duodenum in Normal Human Subjects and in Patients with Thyroid Disease was recorded by James Christensen, Harold P. Schedl and James A. Clifton[6] (Univ of Iowa). The assembly used consisted of (1) a segment of insulated cable; (2) a silver, silver-chloride KCl salt-bridge electrode at the tip of the cable; (3) a 1-ml. capacity water-filled balloon attached next to the electrode; and (4) a water-filled tube leading from the balloon to a recording device. Electric contacts between the KCl solution inside the capsule and the outside was provided by boring a 1-mm. hole through the capsule and plugging it with cotton.

(6) J. Clin. Invest. 43:1650-1657, August, 1964

The tube assembly was passed perorally and its electrode tip positioned in the duodenum The circuit was completed by means of a standard ECG skin electrode on the abdomen.

Previous studies had shown that intact intestinal muscle exhibits a constant sinusoidal pattern of electric activity, commonly called the slow wave or basic electric rhythm The frequency of this rhythm is remarkably constant and, except for catecholamines and morphine, is little affected by drugs The frequency of the electric waves, however, is decreased by hypoxia or hypothermia Superimposed on the basic electric rhythm are fast bursts of electric potential, often associated with intestinal motor activity

Previous studies of the basic electric rhythm in the intestine of man used needle electrodes inserted into the intestinal muscle, and thus had to be carried out under anesthesia or on surgically created ileal buds or bladders. The use of an intraluminal electrode avoided these artifacts but was subject to other problems, such as relative movement of the electrode and nearby mucosa under the influence of motor activity or respiration To avoid these sources of artifact, frequency of the basic electric rhythm of the duodenum was measured only during breath-holding and during periods when the balloon record indicated absence of motor activity

The validity of recording the basic electric rhythm of the intestine with an intraluminal probe was evaluated by studying isolated dog intestine simultaneously with an intraluminal probe and with an intramurally placed electrode. The records, although not identical, were similar and exhibited the same wave frequency. Other studies suggested that intimate contact of the intraluminal electrode with mucosa is not necessary for qualitative recording of the basic electric rhythm, but that the form of the wave may be determined by the distance that separates the silver, silver-chloride junction from the source of the electric activity

The mean basic electric rhythm frequency in a group of 37 normal adults was 11.73 cycles per minute (S.D. ± 0.45 cycles per minute). This frequency was not affected by the duodenal site from which the record was obtained nor by duration of fasting before the tests. There was a suggestion, however, that frequency was somewhat slower in older subjects. In a group of 24 patients referred for study of abnormal thyroid function, excellent correlation was demonstrated

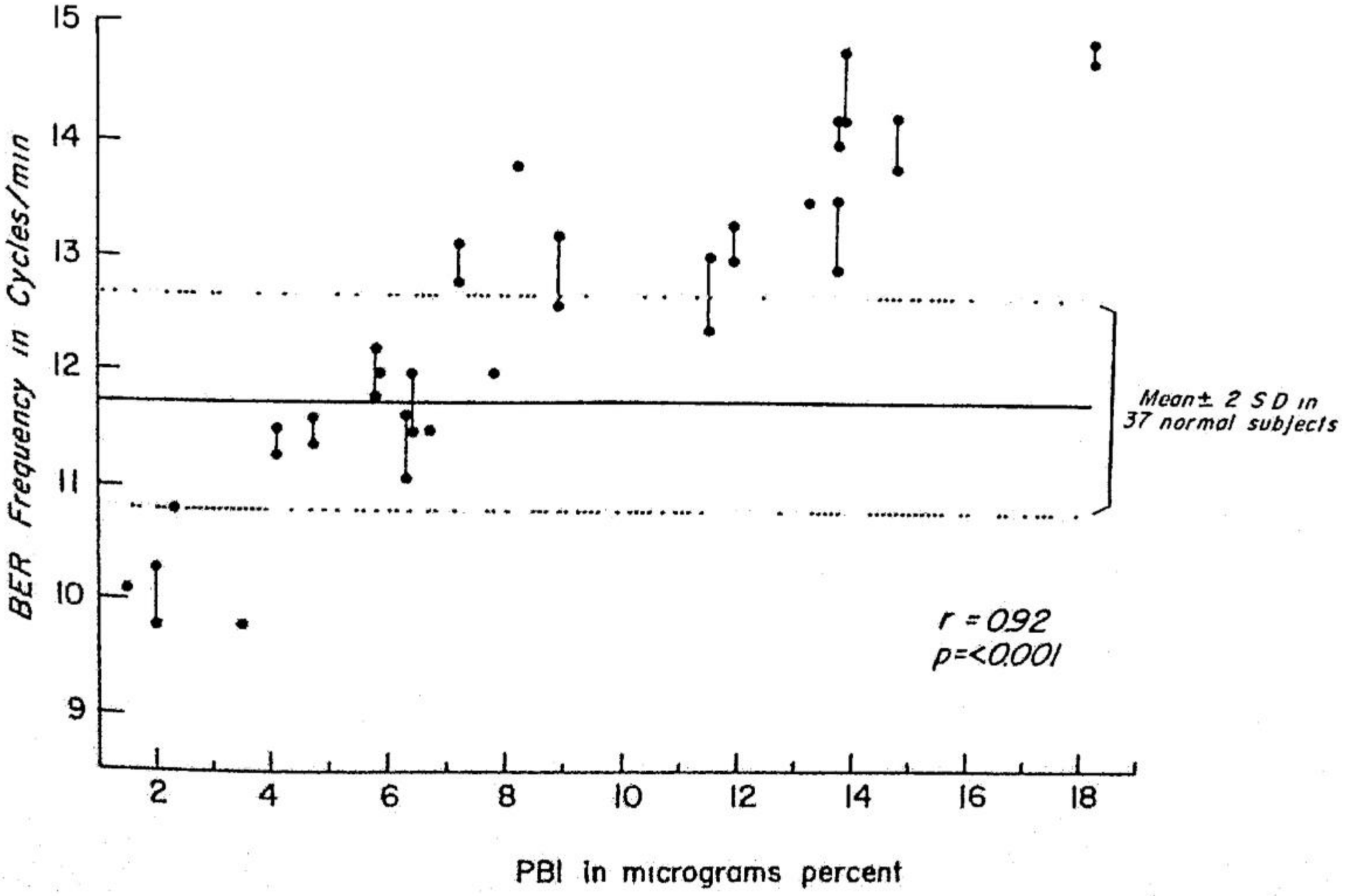


Fig. 56 – Basic electric rhythm (*BER*) frequency and serum protein-bound iodine (*PBI*) concentrations in patients evaluated for thyroid function. (Courtesy of Christensen, J., *et al.* J. Clin. Invest. 43: 1659-1667, August, 1964.)

between the frequency of the basic electric rhythm and the serum protein-bound iodine (Fig. 56).

Although the precise mechanisms responsible for the phasic transmembrane potential of smooth muscle are unknown, they include forces that depolarize and repolarize and that constantly oppose each other in such manner that one alternately exceeds the other. The rate of energy supply must be important in this balance of forces, and it is reasonable, therefore, that thyroid function and metabolic rate should influence the frequency of the basic electric rhythm.

► According to a study by Bass and Wiley (Am. J. Digest. Dis. 10:183, 1965), the basic electric rhythm (BER) is myogenic and has its genesis in the longitudinal muscle. Spike potentials, superimposed on the BER, take place when the circular muscle contracts. Thus, the BER would seem to be unrelated itself to any contractile or tonic activity but provides a control mechanism determining when potentials setting off contractions of circular muscle may be discharged. The prevalence and intensity of the discharges may in turn be under the influence of several humoral factors (see the editorial comment p. 380).

The electric activity that may be recorded from the gut is complex and may have several rather than a single source. Its character is affected not only by various physiologic activities but also by the methodology of recording and the artifacts to which the methodology is exposed. This would seem to be especially true when the potential difference between the gut lumen and the belly wall is being measured. Christensen and his associates can argue, however, that the factual quality of their records is sufficient to dispel theoretical doubt. In par-

ticular, the slowing of the BER in hypothyroidism is a convincing and original observation It may well be related to the substance of the following article —Ed]

Myxedema Ileus. Paralytic ileus secondary to myxedema is a rare cause of intestinal obstruction but one which should be recognized because it is a condition in which surgical intervention could be disastrous R D Hohl and R K Nixon[7] observed a case and found 3 others on reviewing the records of 89 cases of myxedema seen at the Henry Ford Hospital

Woman, 73, was admitted because of inability to walk, urinary incontinence, progressive lethargy, dryness of skin, cold intolerance and severe constipation The skin was cool and dry, the hair thin, the thyroid not enlarged and the abdomen distended Myoedema was demonstrated over the proximal muscles of the arms Neurologic examination revealed a moderate degree of left hemiparesis

Significant laboratory studies revealed protein-bound iodine, 1 1 μg /100 ml , cholesterol, 500 mg 100 ml , radioactive iodine uptake, 2% and basal metabolic rate, −34 Radioiodine uptake did not increase after thyrotropin administration, thus establishing diagnosis of primary myxedema

The patient did rather poorly and seemed to be on the brink of hypothermic coma On the 19th hospital day, marked abdominal distention developed There were no abdominal sounds, and a flat plate of the abdomen revealed gross dilatation of both large and small bowel A barium enema revealed adynamic ileus Successful treatment was carried out by decompressing the small intestine with a long intestinal tube and giving parenteral therapy After appropriate treatment for hypothyroidism, she gradually improved At this stage, a second barium enema yielded normal findings except for a lack of haustral markings

Atony and hypomotility of the gastrointestinal tract are widely recognized concomitants of myxedema and are responsible for distention, flatulence and stubborn constipation. A less well-recognized derangement is a megacolon which can simulate Hirschsprung's disease. In addition, mega-esophagus and localized enlargement of the duodenum, stomach and small bowel have been described The ultimate expression of severe myxedema is paralytic ileus with signs of intestinal obstruction, although occasionally intestinal paresis may be the first symptom of an unrecognized hypothyroidism If the condition is correctly diagnosed, conservative management of the distention and thyroid substitution therapy can be expected to be successful.

► [An excellent discussion of the hypothyroid bowel is to be found in the "Case Records of the Massachusetts General Hospital" (New England J Med 272 1118, 1965) Apparently, adequate treatment of hypothyroidism does not necessarily produce correspondingly improved bowel function, for as J B

(7) Arch Int Med 115 145 150, February 1965

Stanbury points out, "Thyroid disease is not reversible except in terms of replacement of the hormone that the gland is not making One does not cure the fundamental disease "

The distinction that must thus be made between certain basic tissue changes characteristic of hypothyroidism on one hand, and changes in function related to the decreased metabolic rate on the other, might apply to hypothyroid megacolon and myxedema ileus, respectively Apparently, the slow basic electric rhythm of the duodenum in patients with hypothyroidism reflects the low metabolic rate, for J A Clifton reports (personal communication) that proper treatment speeded up the BER in hypothyroid patients. Whatever the mechanism, the relation of the slow BER in hypothyroidism and the intestinal disorders found in that condition is a cause for interesting speculation

The most extensive report of paralytic ileus in hypothyroidism is that of Bastenie (Lancet 1:413, 1946) —Ed]

Variations in Small-Intestinal Villous Shape and Mucosal Dynamics are discussed by B. Creamer[8] (St. Thomas's Hosp., London) who examined 20 small-intestinal biopsies taken from patients who had a variety of gastrointestinal disorders but did not have idiopathic steatorrhea. The sections were examined under the dissecting microscope and graded as follows: grade 1, finger villi; grade 2, finger villi and leaf-shaped villi mixed; grade 3, leaf-shaped villi; and grade 4, ridged convolutions (Fig. 57). By means of conventional microscopy, counts of at least 2,000 epithelial cells were made of young crypt cells, adult cells on the villi and metaphase mitotic figures. From this a ratio of adult cells to crypt cells was calculated, the mitotic rate was expressed as metaphases per 100 crypt cells. In the case of leaf-shaped villi, cell counts were made on sections cut through the short axis. Total mucosal height was also measured. Comparison of four of these measurements showed good correlation between dissecting microscope appearance and the adult cell to crypt cell ratio (Fig. 57).

The average mitotic rate was 1.1% in the normal crypts and 0.9% in the abnormal specimens. When crypt length was short, the mitotic rate was low and averaged 0.6%, but in specimens showing long crypts, the rate was normal, 1%.

Since finger-shaped villi have large and leaf-shaped or convoluted villi and have a small mucosal cell population, villous shapes may merely reflect the availability of mucosal cells. When these are abundantly available, fingers are formed, but when the supply of such cells is sparse, leaves and ridges necessarily form to create supporting structures. Thus, the balance of cells produced and lost dictates the villous shape.

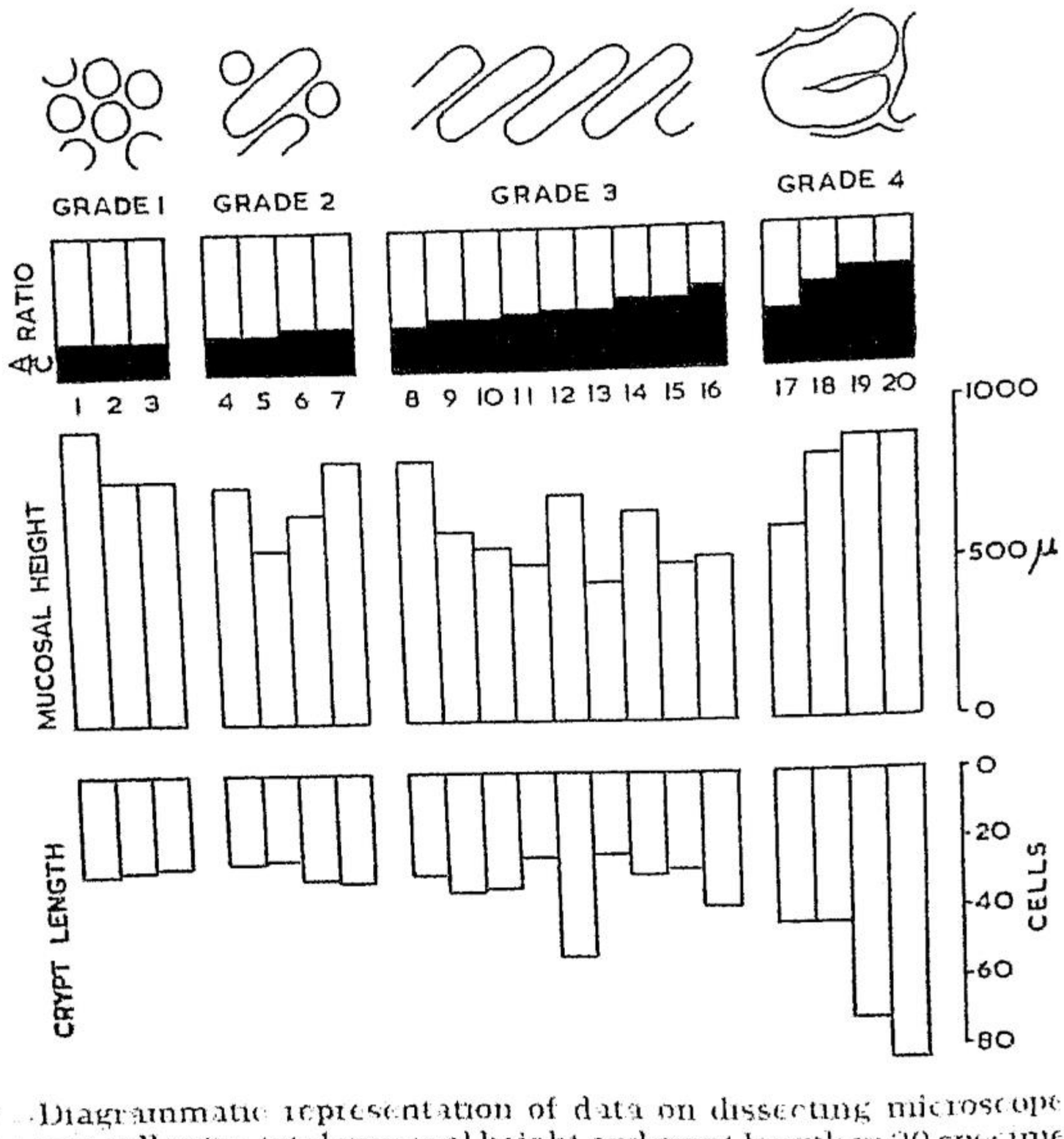


Fig 57 -Diagrammatic representation of data on dissecting microscope appearance adult cell to crypt cell ratio, total mucosal height and crypt length in 20 specimens (Courtesy of Creamer, B Brit M J. 2 1371-1373 November, 1964)

An analogy may be drawn between the responsible pathologic mechanisms and those believed to characterize various types of anemia The intestinal mucosa in idiopathic steatorrhea, for example, is flattened because of a maturation arrest of crypt cells In other cases, which show a small adult cell population but an increased population of crypt cells, the process may resemble bone marrow hypertrophy in response to hemolysis in that hyperactivity of the crypt population compensates for excessive loss of surface mucosal cells. Finally, a group of abnormal mucosae showing normal or shortened crypt length and diminished mitotic rate may be compared with bone marrow hypoplasia

Changes in villous structure and in size of mucosal cell populations may impair absorption by two mechanisms The mucosal surface area may obviously be decreased Second, when adult cells are shed into the gut lumen at an excessive rate, the cell turnover may be so fast that the cells covering the villi may be immature with respect to their enzymatic content.

► [Creamer illustrates his thought-provoking speculations in two other arti-

cles In one (Brit M J 2·1373, 1964), he describes the characteristics of specimens of small intestinal mucosa obtained from a variety of conditions believed to change the cellular luminal environment, i e , conditions such as gastroenterostomy, chronic intestinal obstruction, chronic pancreatitis, and Zollinger-Ellison syndrome All these specimens had a small adult but an increased crypt cell population, thus providing examples of his "hemolytic" mechanism of abnormal cell turnover In the second (Brit M J. 2·1435, 1964), he reports on the appearance of the small intestinal mucosa of 9 patients with malignancy, in 6 of whom the primary growth was outside the gastrointestinal tract In 6 of the cases, abnormal patterns were seen, interpreted either as hypoplasia of the mucosa or as the type of maturation arrest found in idiopathic steatorrhea – Ed]

Intestinal Absorption: Changing Concepts and Ideas with respect to sugar transport are discussed editorially by T. Z. Csáky[9] (Univ. of Kentucky). Glucose absorption has for some time been considered a specific and complex phenomenon, because it has the capacity to go "uphill," i.e., absorption can take place against a concentration gradient, and glucose and galactose are absorbed considerably faster than other sugars of identical or even smaller molecular size. Verzár postulated that these phenomena could be explained by phosphorylation of the actively absorbed sugars, and he supported this hypothesis by showing that sugar absorption was inhibited when the tissues were exposed to iodoacetate. Since that time, however, it has been shown that iodoacetate is not a specific poison of phosphorylation, but rather acts as an inhibitor of intermediary carbohydrate metabolism. It was also shown that an unnatural sugar with a methyl group in the third position (3-O-methylglucose) could be absorbed without any phosphorylated compound of 3-methylglucose being identifiable, and even sugars such as 6-deoxyglucose, which are so constituted that phosphorylation is not possible, can also be absorbed.

With increasing acceptance of the concept that the cell membrane consists of lipoprotein, it became necessary to postulate some mechanism that could account for the rapid transfer of certain water-soluble sugars across a membrane relatively impermeable to nonlipid material. The hypothesis is that sugars temporarily become fat soluble by combining with a substance called a "carrier" in the cell membrane. The chemical nature of this carrier is not known, nor has it been isolated, but the kinetics of transport suggest that a true combination occurs between carrier and substrate, just like the temporary combination of an enzyme with its substrate. The postulated carrier is highly specific with respect

[9] Gastroenterology 47:201-205, August, 1964.

Fe from the luminal contents. The increase in the divalent mucosal pools was quantitatively the same in both groups, but the trivalent pool increase was much more striking in the animals given iron and accounted for 85% of the iron taken up by the mucosa. Thus, in vivo as in vitro, a dose of oral Fe decreased subsequent absorption with diversion of mucosal iron to a trivalent pool.

The time course in vivo was studied by giving iron to rats and killing them at various intervals thereafter. Both mucosal iron pools were markedly increased 1 hour after the dose. By 2 hours, divalent and trivalent pools were decreased by 62 and 45%, respectively, and thereafter approached control values slowly. Experiments showed that disappearance of iron from the mucosal pools was chiefly by absorption into the blood stream and not by loss into the intestinal lumen.

Figure 58 illustrates the pathways of iron transport across the duodenal mucosa in the rat and shows how the mucosal Fe^{++} pool may serve as a depot or "sink" for storing excess iron within the mucosa. The Fe^{++} pool is available for subsequent absorption into the blood stream, although at a slower rate than Fe^{++}, and it is probable that Fe^{+++} must be converted to the divalent form prior to transfer out of the mucosa.

In the presence of dietary iron excess, the mucosal trivalent pool is enlarged, and absorption is slowed because trivalent mucosal iron must be mobilized and converted to the divalent form and the transport mechanism (mucosa to serosa) may be inhibited by an unknown mechanism. This mechanism is apparently a primary effect which may be called "self-inhibition." It does not appear to be related to ferritin, because the amount of mucosal apoferritin measured in these experiments could not account for more than 8% of the Fe^{+++} pool. In the case of chronic dietary iron excess, the persistently increased trivalent pool might account for some iron loss into the intestine when epithelial cells are sloughed off at the tips of the villi.

► [As this and the following article illustrate, the mystery of what controls iron absorption remains unsolved, but individual mechanisms that may participate in the over-all control of iron absorption are being identified and evaluated as to their importance. Crosby and his group believe that the iron content of the intestinal epithelium, which can exchange readily with iron elsewhere in the body, plays a determining role (J. Clin. Invest. 43: 963, 1964), a view supported at least in part by Bothwell's laboratory (ibid. 44: 543, 1965). This latter group, however, would disagree with the idea that ferritin bound iron in the mucosa is of little consequence. — Ed.]

mucosal Fe^{++}, 18.3; mucosal Fe^{+++}, none; underlying coats Fe^{++}, 9.1; and underlying coats Fe^{+++}, 4.7. When everted duodenal segments from previously untreated rats were incubated in the iron-containing medium, Fe^{++} was absorbed rapidly into a mucosal Fe pool and subsequently transported in part to underlying coats and serosal medium. This transport appeared specific for Fe^{++} because 87% of the iron in the coats and serosal medium was in this form. During uptake of Fe^{++}, a mucosal Fe^{+++} pool formed slowly; subsequently, when iron uptake had ceased, a slow increase of the trivalent mucosal pool took place at the expense of the divalent pool.

When segments from rats previously dosed with iron were tested, the baseline mucosal pools for Fe^{++} and Fe^{+++} were 104 and 169 mμM. per segment, respectively, and the initial velocities of mucosal uptake and transport of Fe were decreased by 56 and 95%, respectively. This transport defect was associated with increased conversion of mucosal Fe^{++} to mucosal Fe^{+++}. These data, and in particular the specific activity of the di- and trivalent pools, suggested that the mucosal divalent pool is the precursor of the trivalent pool and that transport from the mucosa toward the serosa is specific for divalent iron.

Duodenal loops were also prepared in vivo and filled with medium similar to that used for the in vitro experiments. The loops were excised after 30 minutes and drained, and the mucosal iron pools, tissue Fe^{59} and residual iron and Fe^{59} in the luminal contents were determined. When results in rats previously given iron and in control rats were compared, prior oral Fe intake decreased the subsequent net uptake of

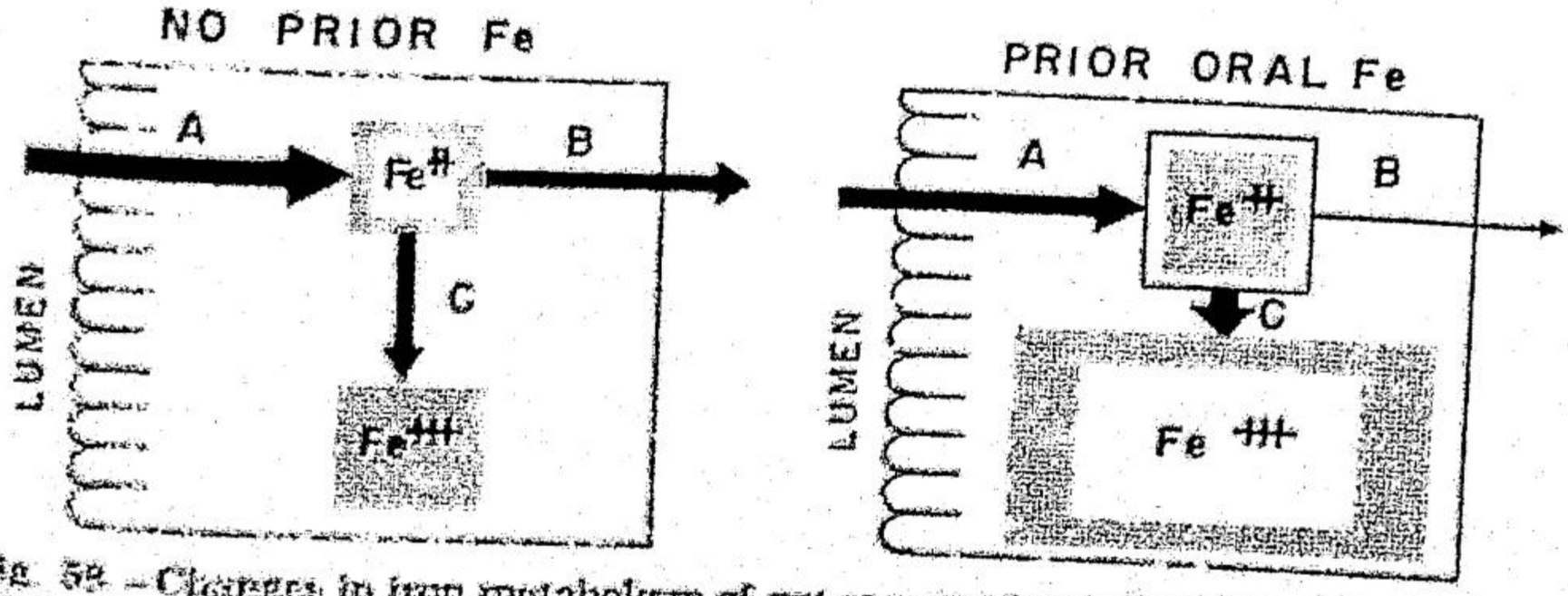


Fig. 52.—Changes in iron metabolism of gut sacs in vitro induced by prior dose of 4 mg. of oral Fe. Width of arrows for mucosal uptake (*A*), transport toward serosa (*B*) and diversion to circulating pool (*C*) represent net values observed after 2½ hours of incubation. Light areas represent the mucosal Fe^{++} or Fe^{+++} pools before incubation and dark areas, the corresponding pools after incubation. (Courtesy of Marine, J., and Schachter, D.: Am. J. Physiol. 207: 623-628, October, 1964.)

Edith Mankiewicz and Jean Béland (Montreal) Guinea pigs infected with only 1 μg of tubercle bacilli and with mycobacteriophage DS6A showed a smaller number of more discrete lesions than did those inoculated with the same amount of tubercle bacilli only However, animals in the former group died at a faster rate Administration of hydrocortisone orally, 1 mg/100 Gm. body weight every 2d day for 7 weeks, to the phage-infected animals increased the numbers of lesions but, at the same time, lowered their allergic state and lengthened the period of then survival

Simultaneous infection with tubercle bacilli and mycobacteriophage DS6A gave rise to homologous and heterologous phage antibodies The level of homologous antibodies was below detection in animals given cortisone However antibodies to bacteriophages with a broader lytic spectrum, and especially antibodies to phage Leo, can be demonstrated in the serum of these animals From the granulomatous sarcoid-like lesions of guinea pigs infected with DS6A and tubercle bacilli (Figs. 24 and 25), "atypical" strains of mycobacteria were isolated, either alone or with typical Mycobacterium tuberculosis. Some of these strains produced lytic phage particles When, after repeated subculturing, these bacteria were inoculated into normal guinea pigs, they determined inflammatory reactions, but no sarcoid-like lesions The observations suggest that sarcoid like lesions are caused by a transitory form of mycobacteria which emerges by lysogenization, and from the selective action of phage antibodies

▻ [The possibility of some pathogenetic relationship between mycobacteria and sarcoidosis has tantalized microbiologists and clinicians virtually since the disease was recognized as an entity distinct from tuberculosis Whether mycobacteria and mycobacteriophages are similarly related to human sarcoidosis as they are to these experimentally induced lesions is, of course, yet far from established but this approach to unraveling the mystery of sarcoidosis seems a promising one As the authors point out, recent epidemiologic observations of Edwards and Palmer indicate a preponderance of reactors to tuberculin prepared from atypical mycobacteria in areas of sarcoidosis prevalence, and Chapman (see the 1962 1963 YEAR BOOK, p. 170) has demonstrated antibodies against atypical (unclassified) strains in the serums of a high proportion of patients with sarcoidosis.—Ed.]

Sarcoidosis Involving the Pleura has been reported in 9 cases, only 1 of which was histologically confirmed Paul J Kovnat and Robert F Donohoe[6] (Washington, D. C.) report 2 additional histologically documented cases

(5) Am Rev Resp Dis 89:707-710, May, 1964
(6) Ann. Int. Med. 62:130-134, January, 1965

Effect of Transferrin Saturation on Iron Absorption in Man is negligible, according to Munsey S. Wheby and Genoveva Umpierre[2] (Univ. of Puerto Rico). Five essentially normal subjects were given orally administered test solutions containing ferrous sulfate and about 8 μc. of radioactive ferrous citrate. Surface-counting rates were obtained over the liver 90-150 minutes after the test dose was given, and serial samples of blood were taken for measurement of plasma radioactivity, iron and iron-binding capacity. After 9-10 days, the test was repeated. Before one of each pair of absorption tests, a sterile and nonradioactive solution of ferrous ammonium sulfate and ascorbic acid was given intravenously over 10 minutes in an amount estimated to saturate circulating transferrin. A maintenance dose of 4.5-9 mg. iron per hour was then continued until the study was terminated. In many studies, saturation was temporarily exceeded, as indicated by facial flush, sneezing or a sensation of warmth or nausea.

During the control studies without transferrin saturation, only 1 of 5 subjects accumulated radioactive iron in the liver. In contrast, 4 of the 5 studied during transferrin saturation had significant accumulation of radioactive substance in the liver. Peak plasma radioactivity was 4 to 53 times higher in the control experiments, indicating that more absorbed iron reached the peripheral circulation when transferrin was not saturated.

Similar experiments were carried out in 2 patients with portacaval shunts. In neither was saturation of transferrin followed by accumulation of radioactive iron in the liver. In 2 normal subjects whose transferrin had been saturated, the subject's own plasma previously tagged with Fe^{59} was injected intravenously. Although some radioactive iron accumulated in the liver after intravenous injection of such transferrin-bound Fe^{59}, the increase in hepatic radioactivity was much less than after oral administration of radioactive iron to the same subjects when their transferrin was saturated.

In 2 other subjects, whose iron-binding capacity had been saturated, free iron injected into the blood was rapidly lost from the circulation and was only in part available for subsequent hemoglobin synthesis. If, however, the iron had

previously been incubated with a plasma sample containing unsaturated transferrin, the iron so injected in bound form was normally distributed in the plasma and was incorporated into the red cells subsequently. In neither of these two procedures did the radioactive label accumulate in the liver.

In human subjects, as well as animals, iron absorption continues despite complete saturation of transferrin. When transferrin is saturated, however, the absorbed iron is principally deposited in the liver on the first circulation and does not reach the peripheral blood. When the liver is bypassed, as in patients with portacaval shunt, deposition in the liver does not occur. Thus when insufficient transferrin is available to bind iron being absorbed, the newly absorbed iron behaves as free ionic iron and is lost from the circulation into the first capillary system encountered. In view of these facts, absorption studies based on isotopic analysis of peripheral blood are invalid when transferrin is highly saturated.

Cystinuria: Defective Intestinal Transport of Dibasic Amino Acids and Cystine. S. O. Thier, S. Segal, M. Fox, A. Blair and L. E. Rosenberg[3] (Nat'l Inst. of Health) performed peroral biopsies of intestinal mucosa near the ligament of Treitz in 18 normal subjects and 12 patients with cystinuria. The biopsy specimens were incubated in a physiologic medium containing S^{35}-labeled cystine or C^{14}-labeled L-lysine, L-arginine or glycine, and the distribution ratio of the test amino acid in intracellular fluid and in ambient medium was determined at various intervals. In this system, a distribution ratio exceeding 1 was accepted as evidence of accumulation of amino acids within tissue against concentration gradients.

In biopsy specimens from normal subjects, the distribution ratios for amino acids approached constant values after 30-45 minutes, mean values for these ratios being: lysine, 14; arginine, 29; cystine, 5; and glycine, 5. These accumulations of amino acids appeared to be energy dependent since they did not occur if the tissue sections were incubated anaerobically or if 2,4-dinitrophenol was added to the incubating medium As the concentration of cystine or lysine in the incubating medium was increased, the rate of accumulation of amino acids approached a maximal value, indicating that the transport mechanisms were behaving as saturable systems. On the basis of rates of uptake during the phase of

(3) J Clin Invest 44 442-448, March, 1965

rapid accumulation (within the first half-hour), the apparent affinity constant for lysine transport was calculated to be 2.5 mM. and for cystine transport, 0.71 mM.

In 10 of the 12 patients with cystinuria, uptake of cystine, lysine and arginine by the intestinal mucosa was markedly impaired, distribution ratios for each of these three amino acids being 3.0 or less. Glycine uptake, however, was normal. In 2 of the cystinuric subjects, lysine and arginine uptake was only moderately depressed, and cystine uptake was normal.

Experiments were carried out with specimens of normal intestinal mucosa to discover whether amino acid uptake was inhibited by presence of unlabeled amino acids. Lysine accumulation was inhibited by arginine and cystine but not by glycine. Cystine accumulation was inhibited by lysine but not by glycine. Failure of glycine to inhibit transport of either cystine or lysine suggests that the inhibition observed had some degree of specificity.

In the gut, cystine, lysine and arginine transport are defective in cystinuria. According to previous studies, however, human kidney cortex slices from cystinuric subjects show normal cystine accumulation but abnormal uptake of lysine and arginine. Thus, although the intestine appears involved in cystinuria, the defect in intestinal and renal tissue is different. These findings are consistent with reports in the literature that intestinal and renal handling of cystine and the dibasic amino acids differs in different animals. Furthermore, it has been reported that plasma cysteine rather than cystine might be the source of urinary cystine in cystinuria.

The finding that 2 of the patients had intact intestinal transport mechanism for cystine and only partially defective uptake of lysine and arginine may be explained by postulating that the defect in these 2 patients was genetically heterozygous rather than homozygous

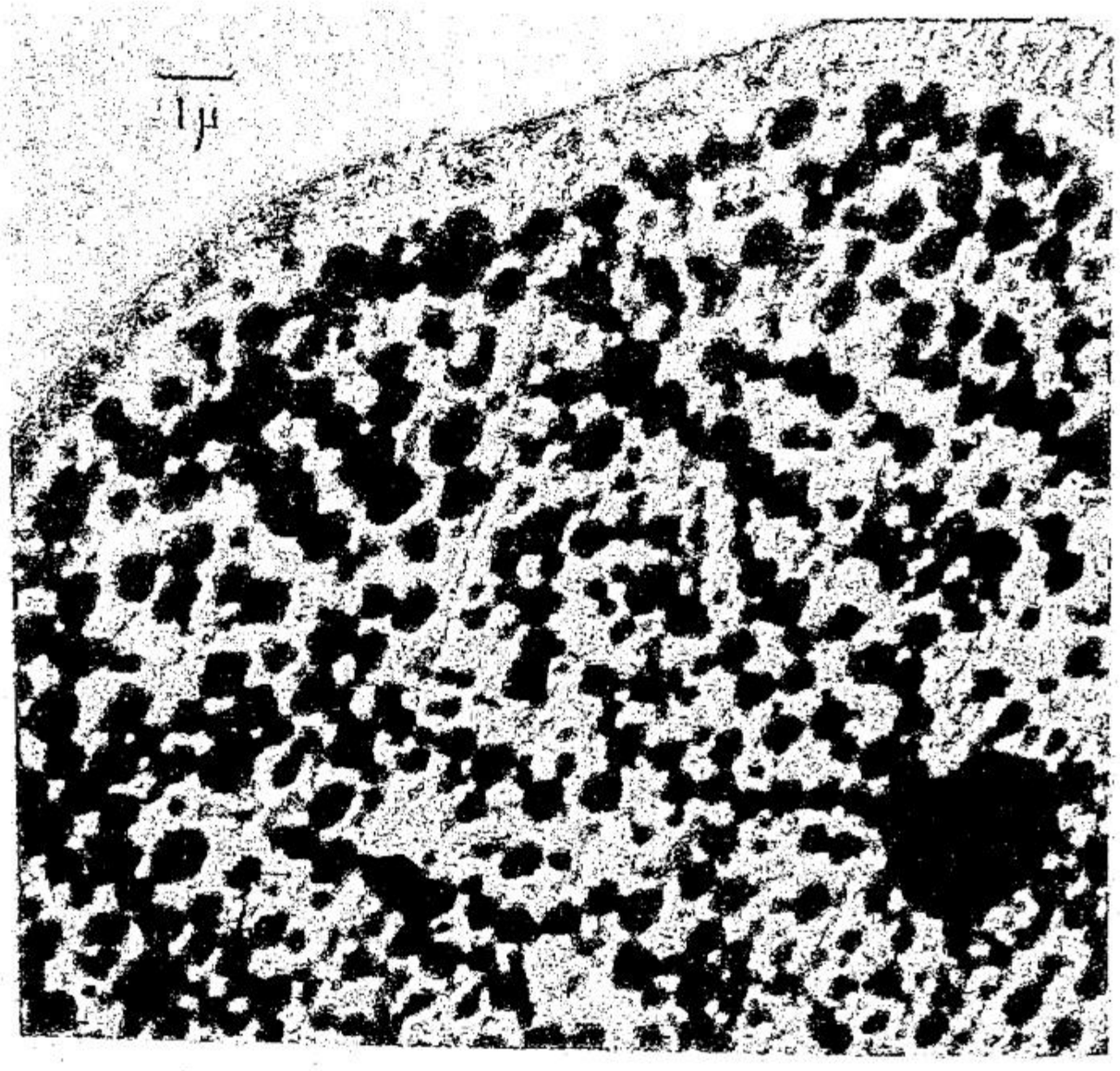
Protein Synthesis Inhibition: Mechanism for Production of Impaired Fat Absorption. The absorption of dietary triglyceride involves the formation of chylomicrons, which contain, in addition to their lipid components, a protein moiety making up 0.5-2% of the weight of the particle. In spite of its smallness, this moiety is probably essential for the movement of lipid out of the mucosal cell into the lympatics. For example, an hereditary deficiency of β-lipoproteins produces

a striking defect in the movement of lipid out of the intestinal mucosal cells. A similar defect in lipid transport was produced in rats by Seymour M. Sabesin and Kurt J. Isselbacher[4] (Massachusetts Gen'l Hosp.) by the administration of puromycin and acetoxycycloheximide, agents that inhibit protein synthesis.

When normal rats were given corn oil by intubation, lipid droplets accumulated rapidly within the villous epithelial cells, but 4 hours after administration, most of the stainable lipid was within villous and submucosal lymphatics, and 6 hours after, lipid droplets in the mucosa were sparse. In contrast, rats pretreated with puromycin showed progressive accumulation of fat within the intestinal epithelial cells. These cells were still heavily laden with lipid droplets 6 hours after oral administration of corn oil (Fig. 59). Analysis of the mucosal lipid by thin-layer chromatography revealed that it was predominantly triglyceride. In these rats, furthermore, plasma triglyceride failed to rise after corn oil was given. Similar effects were produced when rats were pretreated with acetoxycycloheximide.

Other absorptive processes were not affected by the protein inhibitors. Thus, puromycin-treated rats exhibited normal

Fig. 59.—Electron micrograph of small intestinal villous epithelial cells 6 hours after administration of 1.5 ml. corn oil in a rat treated with 15 mg puromycin. (Courtesy of Sabesin, S. M., and Isselbacher, K. J. Science 147: 1149-1151, Mar. 5, 1965.)



(4) Science 147: 1149-1151, Mar. 5, 1965.

blood glucose curves after oral administration of glucose, the uptake of C^{14}-alanine by intestinal slices was not depressed and incorporation of C^{14}-palmitate into the mucosal lipids was not affected. In addition, no ultrastructural abnormalities of the intestinal epithelial cells were evident on electron microscopy.

The data indicate that inhibition of protein synthesis does not affect the initial phases of lipid absorption but does inhibit the final phase, namely the assembly of the chylomicron which permits ordinary dietary fats to enter the lymphatics. Specifically, the formation of β-lipoproteins appears to be inhibited, for the plasma of puromycin-treated animals showed low values of these substances whereas α-lipoprotein levels were unchanged.

Studies Establishing Absorption of Bromelains (Proteolytic Enzymes) from the Gastrointestinal Tract were carried out by Robert D Smyth, Rita Brennan and Gustav J. Martin[15] (Fort Washington, Pa) in an effort to dispel the skepticism toward claims that proteolytic enzymes appear in the blood after they are eaten Bromelain was labeled with radioactive iodine, and the iodinated compound so prepared was shown to have 22% of the proteolytic activity of regular bromelain.

Rabbits were given bromelain-I^{131} intraduodenally at a dose of about 200 mg /kg. At 1-2 hours later, about 6.5% of the total radioactivity administered was present in the blood of the animal, and at 5 hours, 12% of the administered radioactivity was excreted in the urine. Somewhat more than 2% of administered radioactivity could be accounted for by organ analysis, the largest amount (0.8%) being found in the liver.

A third of the bromelain in the blood appears to be adsorbed onto the red cells, and the remainder is in the plasma. The plasma fraction is nondialyzable and trichloracetic acid precipitable, thus indicating it is attached to a large molecule. On the other hand, it is possible that I^{131} is split off the bromelain in the gut, absorbed as iodide and then reattached to some other plasma macromolecule. To test this possibility, plasma of the rabbit given bromelain I^{131} was subjected to electrophoresis. A plasma sample to which bromelain-I^{131} was added was similarly analyzed. Radioactivity in both plasma samples appeared to be located in the same electrophoretic zone, thus

[15] Exper Med & Surg, 22:26-39 January, 1964.

indicating that the radioactive tag was still attached to the bromelain molecule

► [The authors introduce this article (dealing with a proteolytic enzyme derived from pineapple) with the following sentences "Scientific advancement is a game played by the few over the heads of the many Each step forward by the few seems to be matched by a decision on the part of the many to immobility" The beginning, as well as the end of the paper leaves me firmly aligned with the immobile many The experiences with I^{131}-labeled proteins, such as albumin I^{131} in the gut exemplifies the confusing results which may be obtained when the instability of this label is ignored If the authors really had wished to demonstrate the firmness of the bromelain label, a variety of other procedures could have been carried out, such as giving organic I^{131} and showing that it did *not* appear in the same electrophoretic band as the alleged radioactive bromelain in the plasma

It is, of course, highly likely that intact proteins pass to some degree across the intestinal membrane and that this movement may be increased when the intestinal mucosa is abnormal The problem is the extent of this degree Does enough protein pass across so that the oral administration of proteolytic enzymes may be used for clinical purposes? The authors would say that they have demonstrated that the answer to this question is "yes," and they cite others indicating that trypsin is similarly absorbed If so, we certainly should start talking about the entero-systemic-pancreatic circulation of trypsin —Ed]

Intestinal Crypt Lesions in Neonatally Thymectomized Hamsters were studied by Richard C. Hard, Carlos Martinez and Robert A. Good[6] (Univ. of Minnesota) in an effort to elucidate the wasting syndrome (diarrhea, marked weight loss, pancytopenia and immunologic deficiency) that this procedure induces. Histologic and hematologic studies were carried out in 18 weaned thymectomized animals, 3 weeks or older, and the findings were compared with those obtained in litter mates having sham thymectomies and in intact controls.

In 14 animals with the postthymectomy wasting syndrome, two types of intestinal crypt lesions were found. One manifested disorderly proliferation of large vacuolated cells, the process beginning with loss by the Paneth cells of their bright red staining granules. The cellular cytoplasm became pale and nuclear staining decreased, and continued presence of mitotic figures suggested proliferation of the crypt cells. Inflammatory response to these lesions was usually minimal (Fig. 60). The second type of lesion was an inflammation at the base of the crypts, where minute erosions and microabscesses were found. These two lesions were found independently or concurrently; they may be interpreted as the result of abnormal regeneration of crypt cells.

Striking or consistent lesions in other organs of the thy-

(6) Nature, London 204 455-457, October, 1964.

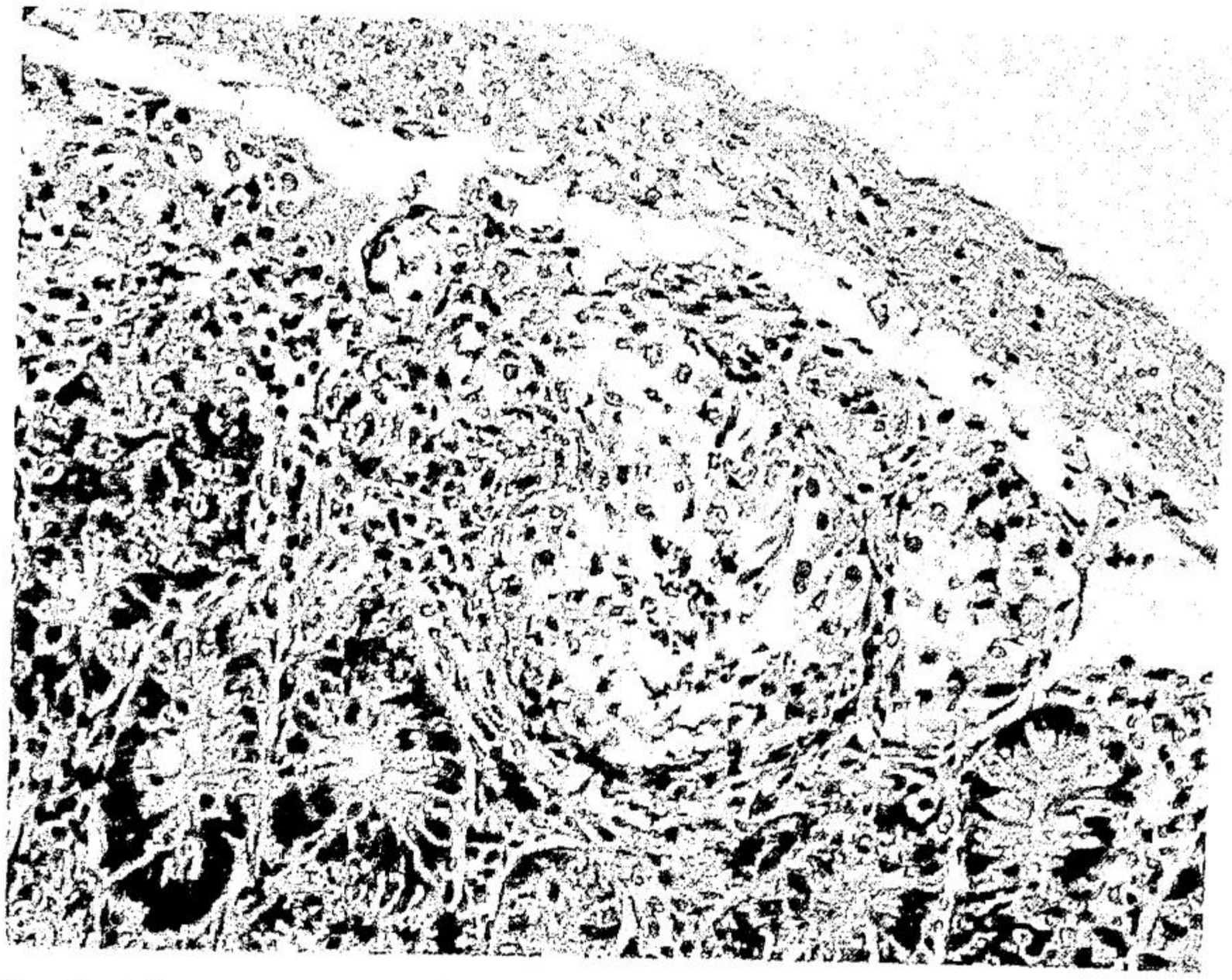


Fig. 60. Proliferative intestinal crypt lesion of neonatally thymectomized hamster. This is an advanced lesion with central cell necrosis and slight acute inflammatory reaction. Note lesser involvement of two adjacent crypts. Hematoxylin eosin. ×133. (Courtesy of Hard, R. C. *et al.*, Nature, London 204: 455-457, October, 1964.)

mectomized animals were not found. However, lymphopenia was found in 16 animals, in which the average proportion of lymphocytes was 6-52% versus a range of 55-90% in control groups. In 13 of the 18 neonatally thymectomized hamsters, both intestinal crypt lesions and lymphopenia were present; whereas coincident lymphopenia and crypt lesions were not found in the control groups. The enteric and hematologic abnormalities may be independent, or the lymphopenia may be responsible for the enteric lesions, possibly because the rapidly proliferating crypt cells need some component normally provided by lymphocytes. It is also possible that the enteric lesions are due to activation of a latent virus. Finally, the lesions may represent direct action of an autoimmune process similar to that seen in animals with homologous disease.

► [This and the following article show how immunologically conditioned processes may damage the gut -- although both groups of authors caution that they cannot exclude a viral infection. -- Ed.]

Runt Intestinal Disease. Runting is a disorder that occurs in the mouse when immunologically competent cells (lymphoid elements) from one strain are grafted to a normal animal of different genetic make-up. Although diarrhea fre-

quently occurs in mice affected by runting, little is known of gastrointestinal involvement in this syndrome. R. W. Reilly and J. B. Kirsner[7] (Univ. of Chicago) studied the course and intestinal pathology of old F_1 hybrid mice injected within 18 hours of birth with 4,000,000 spleen cells obtained from 12- to 24-week old male parents of the hybrids. Some of the host animals were irradiated preceding cell injection. The test animals were killed between the 10th and the 14th days of life, and the intestinal tract was removed and examined in toto.

Gross abnormalities in the small bowel of nonirradiated runted animals were restricted to moderate dilatation of the bowel; its contents were viscous, sticky and tarry black, indicating presence of blood. Microscopically, obvious attenuation and clubbing of the villi were seen. The changes, more marked in the ileum than in jejunum, were at times so extreme that the mucosa appeared colonic rather than intestinal in type. Massive round cell infiltration was absent; indeed, the lamina propria appeared sparsely populated by cells. Cytoplasmic basophilia was evident in the epithelial cells at the tips of the villi, whereas in control animals, such basophilia was limited to small crypt areas.

In animals preirradiated with 100 r, similar structural changes were seen, but they were somewhat more severe. Irradiation by itself, without injection of spleen cells, caused no deviations from the normal. Other control studies suggested that the mucosal changes seen in the runted animals were not merely the result of starvation.

The observed intestinal changes may have been due to a direct cytotoxic effect of the injected spleen cells, exerted either directly or by virtue of an antigen-antibody reaction. The presence of some type of viral infection, however, could not be excluded; bacterial infection appeared unlikely since intestinal cultures from the runted animals and their normal controls showed no difference.

The lack of weight gain, the diarrhea, the sticky intestinal contents and the histologic picture of the intestinal mucosa suggested that runt disease is characterized by malabsorption. Except for the lack of round cell infiltration in the lamina propria, the abnormalities of the mucosa in runt disease resemble those found in sprue.

(7) Lab Invest 14:102-107, January 1965

Acquired Milk Intolerance in Adult Caused by Lactose Malabsorption Due to Selective Deficiency of Intestinal Lactase Activity. Urs Peter Haemmerli, Hansjörg Kistler, Rudolf Ammann, Thomas Marthaler, Giorgio Semenza, Salvatore Auricchio and Andrea Prader[8] (Zurich) studied a group of patients with so-called milk allergy to determine to what extent intestinal lactase deficiency accounted for this disorder. The 24 patients stated to have milk intolerance were divided into three groups. Group 1 comprised 17 controls, 8 of whom had no gastrointestinal symptoms and 9 of whom were suspected of having milk allergy but did not present a convincing history. Group 2 consisted of 4 persons who qualified for bona fide acquired milk intolerance on the basis of the following history: (1) good tolerance of milk in infancy and childhood with later development of intolerance; (2) clear-cut gastrointestinal symptoms such as abdominal discomfort, flatulence, meteorism, pains, cramps and diarrhea consistently within 1 or 2 hours after each milk intake; and (3) absence of symptoms on elimination of milk from the diet. Group 3 consisted of 3 patients with idiopathic sprue.

When 50 Gm. lactose was given in 400 ml. water by mouth, (corresponding approximately to the lactose content of 1,000 ml cow milk and of 700 ml. human milk), the mean maximum rise of glucose in the peripheral blood was 35.1 mg./100 ml in group 1, 6.2 in group 2, and 9 in group 3, indicating defective absorption of lactose in patients with milk intolerance and with idiopathic sprue. When the test dose consisted of a mixture of 25 Gm glucose and 25 Gm. galactose (the products of hydrolyzing 50 Gm lactose in 400 ml water), the mean maximal rises in glucose levels in the blood in groups 1, 2, and 3 were 50, 40, and 28 mg./100 ml., respectively. Maltose tolerance tests produced normal elevations of blood glucose in the control and milk intolerant patients, but lesser elevations in a patient with sprue.

After the oral lactose tolerance test, only 2 patients in group 1 had bowel movements within 8 hours, and these were of normal consistency. All patients in group 2 experienced abdominal discomfort with colicky pains within 30-50 minutes after the lactose load, and urgent evacuation of a watery stool took place within 30-120 minutes. Stool pH was 5.3-6, as opposed to the normal of 7. These stools contained lactose, glu-

[8] Am. J. Med. 28:7-30. January, 1960.

cose and lactic acid. Unabsorbed lactose and glucose act as osmotic laxatives. Further, bacterial fermentation of these sugars produces lactic, acetic, formic, isobutyric and propionic acids, all of which may be irritant to the bowel wall.

Small bowel biopsies appeared normal in groups 1 and 2 and showed the characteristic changes of sprue in group 3 When disaccharidase activity, expressed as units per gram protein of mucosa, was measured, large individual variations were found. It was striking, however, that lactase activity was extremely low in groups 2 and 3, whereas maltase, isomaltase and sucrase activities were within normal range in group 2 but depressed in group 3 Among the normal controls, mean lactase activity was considerably less than the activity of the other enzymes, and the control group, indeed, contained 5 patients with extremely low lactase activity. Re-examination of the lactose tolerance tests in these patients showed that this group, as a whole, had lesser elevations of glucose after the lactose load than the other patients in group 1. Although a correlation between intestinal lactase activity and blood glucose curves after oral lactose loads seemed apparent on inspection, no statistically significant correlation could be made out.

These studies show that some patients with so-called milk allergy have symptoms because of a deficiency of intestinal lactase, but it should be emphasized that only 4 out of some 30 persons suspected of having milk allergy could be identified as having this specific cause. Recognition of those with lactase deficiency depends on historic criteria, flat glucose curves after lactose loads and diminished intestinal lactase activity. Flat glucose tolerance curves, poor responses to lactose loads and diminished mucosal lactase activity, however, are also found in malabsorption conditions such as sprue, and even apparently normal subjects may have low mucosal lactase levels. Apparently normal adults who have low intestinal lactase activity, an inadequate response to lactose tolerance tests or both may be predisposed to milk intolerance. Indeed, 1 of the apparently normal patients who had a low lactase level subsequently became intolerant of milk.

The pathogenesis of acquired lactose intolerance and selective intestinal lactase deficiency in the adult is unknown. In animals intestinal lactase activity is at its peak at

birth and during the suckling period but then falls off. At present, no evidence is available to substantiate a similar decline in intestinal lactase activity in man with advancing age, but some enzymatic adaptation to continued milk intake, or absence of milk in the diet, is possible. It may be suggested as a hypothesis that some adults, particularly those with naturally low intestinal lactase activity, may acquire milk intolerance as a result of exposure to enzymatic inhibitors (which would show no histologic change) or as a result of bacterial, virus or parasitic invasion of the gut.

► [The authors add an addendum stating that their acceptable cases of acquired milk intolerance in adults had increased to 9 Data obtained from studies in these additional patients changed to some extent the average values of intestinal disaccharidase activities and of blood glucose curves following oral disaccharide loads, but the general import of the findings remains unchanged

A deluge of articles on various disaccharidase deficiencies (particularly involving lactase) is inundating the literature The article here abstracted is not necessarily the most up to-date, but it impresses me as the most erudite, and presents, in addition to the findings reported, an excellent review of the absorption of lactose under normal and abnormal conditions Another good review of disaccharide intolerance is that by Littman and Hammond (Gastroenterology 48 237, 1965)

It is noteworthy that apparently normal individuals, with no history of milk intolerance, may respond to lactose loads with relatively flat glucose blood levels and that they may also have low intestinal lactase activity Indeed, as many as a third of "normal" subjects tested show such abnormalities. One must conclude that either the tests are too sensitive and not completely reliable or that borderline and subclinical lactase deficiency is very common —Ed.]

Pathology of Jejunal Mucosa in Tropical Sprue. Virginia L. Swanson and Robert W. Thomassen[9] (San Juan, Puerto Rico) examined 192 jejunal biopsy specimens from untreated adults with tropical sprue The specimens were divided into five categories of abnormality (borderline, mild, moderate, severe and atrophic) and were compared with biopsy specimens classified as normal or as showing nonspecific jejunitis.

Under the dissecting microscope, normal intestinal mucosa exhibits leaf-, tongue- or finger-shaped villi, depending on whether biopsy specimens are taken from the duodenum, upper jejunum or ileum, respectively. Circumferential wrinkles of the villus epithelium are typical. In nonspecific jejunitis and borderline sprue, milk villus swelling is apparent. In mild sprue, the villus swelling is well-developed, thus narrowing the intervillus spaces, and villi are joined in a row to produce leaf forms. In moderate cases, further coalescence of villi takes place to produce convoluted ridges. Intervillus

[9] Am. J. Path. 46 511-551, April, 1965

spaces are reduced in depth, and the mucosal surface resembles the cerebral cortex in miniature. In severe sprue, a flattened, convoluted ridge pattern, grouped into irregular blocks, may been seen In the atrophic variety, no mucosal pattern is evident.

The joining and swelling of the villi do not necessarily progress evenly throughout the gut during the various stages of tropical sprue. Thus the level of the biopsy site, focal patches of disease, rapidity of onset and number of exacerbations and remissions produce considerable variability in the mucosal findings from case to case.

On histologic observation, early predominance of plasma cells, with a few eosinophils, and presence of these cells within villus cores are characteristic features of untreated tropical sprue Although over-all mucosal thickness does not change appreciably, the villus height-crypt depth ratio changes progressively from the normal figure of 4 in the mild cases to 0.1 in the atrophic forms At the same time, the average number of epithelial cells from crypt base to villus tip drops from 140 in the borderline cases to 50 in the atrophic varieties The size of epithelial nuclei in the crypts tends to increase with advancing disease and is about three times normal in specimens classified as severe sprue. Mitotic indexes (mitoses occurring per 100 total epithelial cells in both villi and crypts) are the same in normal specimens and in those classified as severe and atrophic, but the index is markedly increased in mild and moderate cases, being three or four times the normal figure (Fig. 61). A striking feature is progressive increase in argentaffin cell counts, these cells per 100 crypt cells peaking at a value of 2.8 in severe sprue as opposed to a normal value of 0.3. If a correction is made for decrease in total cell population at this stage, argentaffin cells appear to be increased fourfold over normal.

The decreasing epithelial cell count with advancing severity of sprue and the concomitant increase in mitotic index can be explained by postulating prolongation of time required for completion of mitosis, i.e., mild mitosis inhibition. Similarly, the increase in argentaffin cells may not express overproduction but rather inhibition with decreased rate of degranulation. A delay in epithelial cell maturation is also suggested by retention of large nuclei, basophilia of the cytoplasm and suppression of epithelial scalloping. Exposure

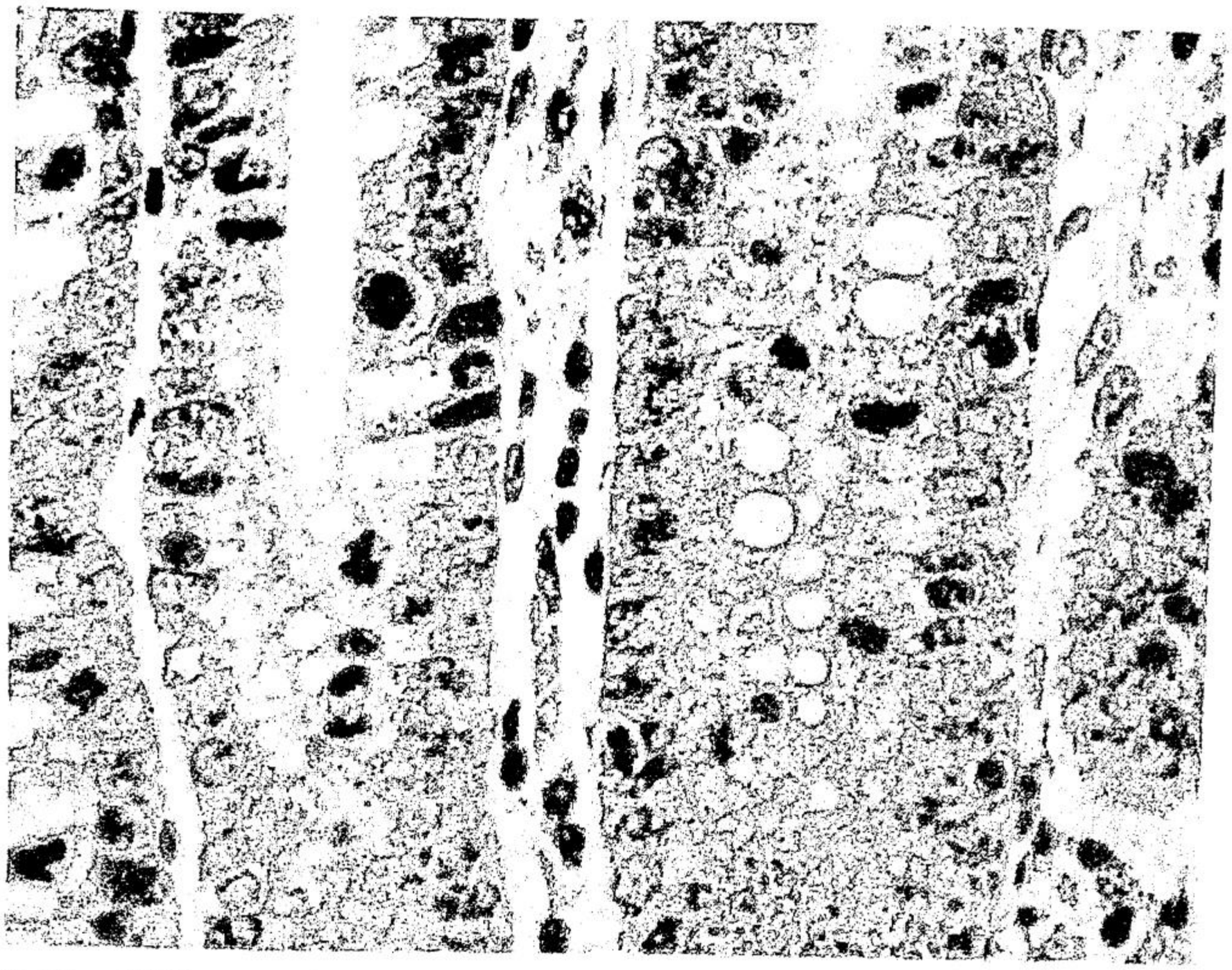


Fig. 61.—Mild tropical sprue (jejunum). Mitotic figures are numerous, crypt cell nuclei are slightly enlarged and some are vacuolated. ×500. (Courtesy of Swanson, V. I., and Thomasen, R. W.: Am. J. Path. 46:511-551, April, 1965.)

of immature or defective cells to chemical and mechanical trauma in the intestinal lumen leads, in turn, to accelerated shedding of these cells from the villi.

Failure of the crypt epithelium to supply adequate numbers of mature epithelial cells for normal villus architecture suggests that tropical sprue is caused by absence of some factor or factors necessary to maintain normal cell proliferation. Possibly the intestinal flora by competitive or other mechanisms may interfere with availability of nutrients, such as vitamin B_{12} and folate, and thus may bring about a disorder which gradually progresses from one representing mild nonspecific jejunitis to one exhibiting the characteristics of tropical sprue. The abnormalities seen resemble those of nontropical sprue or celiac disease in adults in many respects, although limited study indicates that there are more mitoses, less crypt cell changes and fewer argentaffin cells in nontropical than in comparable stages of tropical sprue.

► The observations concerning the mitotic rate do not quite jibe with the figures given by Creamer (see p. 387) but it is obvious that the mitotic count is affected by the stage at which the sprue is seen. It would take studies with tritiated thymidine to determine whether the increased mitotic count is the result of delayed maturation or of an increased cell turnover because of

excessive shedding of epithelial cells into the gut lumen, but the hazards of such testing are too great to permit its use in patients who have benign and curable disease –Ed.]

Absorption of Medium Chain Triglycerides in Tropical Sprue. Since patients with sprue are known to have impaired capacity to absorb naturally occurring triglycerides of animal origin in which 18 carbon fatty acids predominate, Marta Cancio and Rodrigo Menéndez-Corrada[1] (Univ. of Puerto Rico) tested the absorption of medium chain triglycerides in patients with this condition. Medium chain triglycerides containing fatty acids with less than 12 carbon atoms are hydrolyzed in the intestine, then absorbed and transported as fatty acids via the portal vein. The preparation used was derived from coconut oil and consisted of a mixture of triglycerides containing saturated fatty acids ranging in chain length from 6 to 12 carbons; the predominant component was caproic acid. This mixture yielded 8.3 calories per Gm.

On a standard diet containing 106 Gm. fat and normal long chain triglycerides, 2 patients with acute sprue, 4 with sprue in relapse and 2 with sprue in remission excreted from 5.9 to 20.8 Gm. fat a day, the coefficient of fat absorption ranging from 74 to 93%. When the medium chain preparation was substituted isocalorically for the normal fat in the diet, daily fat excretion in these patients ranged from 2.8 to 6.5 Gm. a day, with coefficients for fat absorption ranging from 92.3 to 97%. Further, ingestion of a medium chain triglyceride was accompanied by increases in the serum levels of cholesterol, β-lipoproteins and total serum lipids. In most cases, especially those of acute sprue, rapid weight gains occurred When the normal fat diet was reintroduced in some of these patients, steatorrhea reappeared, and the various indexes of improvement deteriorated.

Medium chain triglycerides have a place in management of sprue. In this condition, transfer of medium chain fatty acids from lumen, to epithelial cell, to mucosal capillary and to liver is apparently unimpaired.

► [The near normal absorption of medium chain triglycerides in tropical sprue is puzzling. As emphasized in the preceding article, the mucosal surface is certainly grossly curtailed in this condition, and the normal absorption of the medium chain preparation in the face of this curtailment would argue that surface area cannot be as much of a factor in limiting fat absorption as it has been thought to be Whether a substance is transported by lacteals or capillaries would seem to be of little consequence when the absorbing surface is shortened by a factor of 10 or more

(1) Proc Soc Exper Biol & Med 117 182 185, October, 1964

The lack of a good rationale to explain the apparent efficacy of medium chain fatty acids in tropical sprue may be related to the fact that the biochemical steps in the absorption of these fatty acids are still uncertain. The authors quote others to the effect that medium chain triglycerides are hydrolyzed in the intestine and then absorbed as fatty acids Studies reported by Playoust and Isselbacher (J Clin. Invest 43·878, 1964), however, suggest that medium chain triglycerides enter the cell as such and are then subjected to intracellular hydrolysis Yet Valdivieso and Schwabe (Gastroenterology 48:331 and 336, 1965) show that the absorption of medium chain triglycerides is impaired in the absence of either bile or pancreatic juice, findings which would favor the view that these triglycerides are hydrolyzed at least in part in the gut lumen –Ed]

Amino Acid Uptake and Fatty Acid Esterification by Intestinal Mucosa from Patients with Whipple's Disease and Nontropical Sprue. Malabsorption in nontropical sprue is usually ascribed to a disorder of the intestinal epithelial cells, whereas in Whipple's disease, in which the major pathologic changes affect the lamina propria, malabsorption is generally ascribed to partial lymphatic obstruction. If these beliefs are correct, intestinal mucosal tissue from patients with Whipple's disease should be able to carry out amino acid transport and fatty acid esterification in near normal fashion. On the other hand, these functions should be markedly impaired when mucosa of sprue patients is tested. Because of these considerations, Robert S. Brice, Jr., Edward E. Owen and Malcolm P. Tyor[2] (Duke Univ.) performed in vitro tests of the metabolic functions of mucosal biopsy specimens obtained from 3 patients with Whipple's disease, 2 patients with nontropical sprue, a group of patients hospitalized with various disorders and 4 healthy volunteers.

Biopsy specimens were obtained from the distal duodenum of patients who had fasted overnight. These specimens were incubated in solutions containing the C^{14}-labeled basic amino acid arginine, lysine or ornithine or the neutral amino acid phenylalanine. Amino acid uptake by the tissue, expressed either as a percentage of the total incubating fluid counts taken up by 10 mg. wet weight mucosal tissue or as the ratio between total radioactivity in tissue water and incubating fluid, was markedly and about equally depressed in the samples taken from the patients with Whipple's disease and those with nontropical sprue. Mean values for arginine uptake, for example, were 10.7% per 10 mg. wet weight by specimens from normal subjects, 6.7% by those from hospitalized controls, 2.2% in nontropical sprue and 2.6% in Whip-

[2] Gastroenterology 45:554-562, May, 1965.

ple's disease. Phenylalanine uptake by the abnormal tissues, however, was only moderately and variably depressed.

To measure incorporation of C^{14}-labeled palmitic acid into triglyceride, mucosal specimens were homogenized and incubated with solutions containing palmitic acid-1-C^{14} and adenosine triphosphate, and the amount of labeled triglyceride formed was separated and quantitated The rate of triglyceride formation by the mucosal homogenates from the control subjects was more than twice that found when specimens from the patients with either sprue or Whipple's disease were used.

The intestinal epithelial cells in the patients with Whipple's disease appeared within the limits of normal by both light and electron microscopy. Thus, although Whipple's disease and sprue are quite different with respect to epithelial morphology, the metabolic functions of the epithelium in terms of amino acid uptake and fatty acid esterification appeared to be strikingly and equally depressed in both conditions. To what extent this finding explains the malabsorption of Whipple's disease is uncertain.

► [The authors suggest various explanations for their results, but an obvious problem is that the metabolism of mucosa as a whole, not just of epithelial cells, is being tested by the methods used, and certainly the lamina propria in Whipple's disease is abnormal structurally as well as functionally However, if the results do apply strictly to the epithelial components of the tissue specimens tested, one might wonder if these cells might not be "saturated" with various nutrients despite their normal appearance In other words, they might resemble normal appearing hepatic cells which, in the face of common duct obstruction, do not take up and secrete a variety of substances normally, even though they appear structurally well preserved One anticipates the development of techniics in which purely epithelial cells may be studied —Ed]

Diabetic Steatorrhea: Distinct Entity. After observing the progressively downhill course of a patient with severe diabetes, postural hypotension and diarrhea, Lawrence D. Wruble and Martin H. Kalser[3] (Univ. of Miami) reviewed the literature for similar patients with both diabetes and steatorrhea. The 26 found fell into two distinct groups, the first apparently having steatorrhea as a true complication of diabetes, and the second manifesting diabetes and nontropical sprue as two independent but associated conditions.

The first group shows a marked male preponderance, only one of the 15 cases being in a woman. The diabetes begins early (mean age, 28 years), is difficult to control and usually precedes onset of diarrhea (mean, 36 years). The major

(3) Am J Med 37 118-129, July, 1964

symptom is diarrhea, often with 20-50 watery movements per day, which differ from the soft, bulky and frothy stools of primary malabsorption. Nocturnal bowel movements and fecal incontinence are common and lower abdominal cramps occasional. Anorexia, nausea and vomiting occur in some cases, usually related to delayed gastric emptying.

On examination, characteristic findings are postural hypotension, peripheral neuropathy, disordered sweating and evidences of degenerative vascular disease. The biochemical abnormalities usually found in other malabsorption states may be absent. Thus anemia tends to be mild and nonspecific, and serum protein, prothrombin and calcium levels are near normal Although steatorrhea may be striking (30-60 Gm. fecal fat per day), absorption tests using xylose or vitamin B_{12} may show no or only moderate impairment. A striking x-ray finding, reported in 4 cases, is delayed gastric emptying Small bowel biopsies, available in only 2 of the cases, show an essentially normal pattern.

No treatment is known that consistently benefits the steatorrhea of diabetes. Agents and methods that have been used unsuccessfully include crude liver extract, folic acid, pancreatin, adrenal corticosteroids, antibiotics, vitamin B_{12}, cholinergic drugs and gluten-free diets. In some patients, including the 1 seen by the authors, diarrhea improves during periods of good diabetic control.

The distinguishing features of the second group, in which diabetes mellitus and nontropical sprue appear to exist concomitantly, are (1) later onset of diabetes (in 6 of 11 patients at age 40 years or more) and onset of diarrhea often preceding that of diabetes, (2) satisfactory to good diabetic control with few neurologic or vascular complications of diabetes, (3) laboratory findings typical of primary malabsorption with impaired absorption of xylose and vitamin B_{12}, (4) typical small intestine mucosa changes on biopsy and (5) good clinical response to a gluten-free diet.

The etiology of the steatorrhea of diabetes (group 1) is not known. Presumably it is a more intense manifestation of diabetic diarrhea, especially since steatorrhea appears to supervene in those patients having the more severe forms of diabetes. Factors that have been considered responsible include vitamin deficiencies, pancreatic insufficiency, bacte-

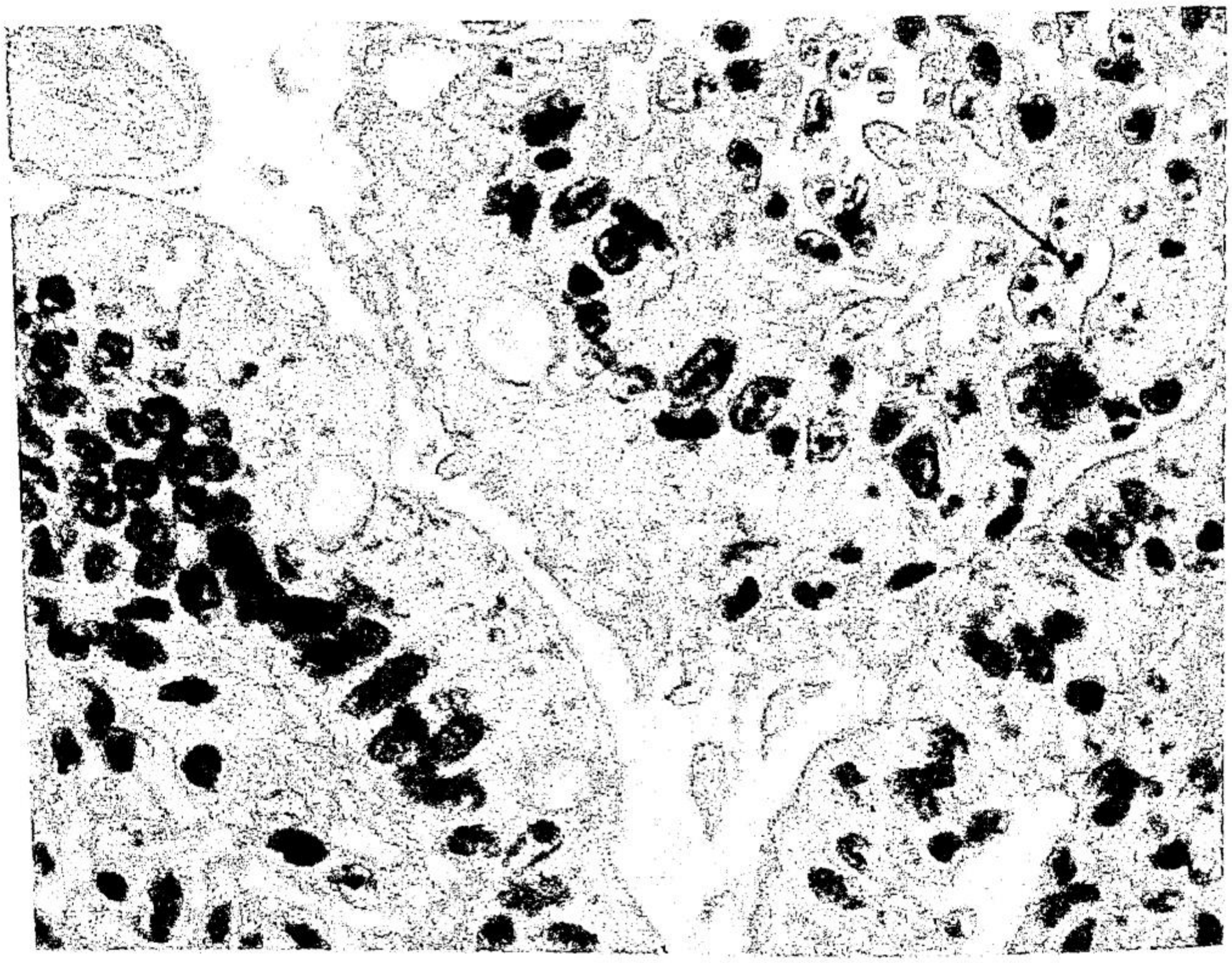


Fig. 62.—Section showing giardia near the base of the villi. Some organisms are closely applied to the epithelium. In one area (*arrow*), polymorphonuclear leukocytes are infiltrating the epithelium; a few have reached the lumen. Hematoxylin-eosin, ×750. (Courtesy of Yardley, J. H., *et al.*: Bull. Johns Hopkins Hosp. 115: 389-406, November, 1964.)

exist as a harmless commensal in many people, the histologic evidence of disease found in the jejunal biopsies of the cases here reported indicates that giardia can be a significant intestinal pathogen. Since giardia do not invade beyond the bowel lumen, some mechanism other than entrance of the parasite into the tissues is needed to explain the associated mucosal lesions. Perhaps the parasite elaborates a toxic substance, perhaps the lesions are the consequence of bacteria or fungi growing in the intestine in association with the giardia; perhaps the giardia impede the normal outflow of secretions from the crypts; perhaps there is an unrecognized tissue phase in the life cycle of the trophozoite, or perhaps the giardia by their very mass may cover the mucosa, thus decreasing the area available for absorption and possibly pre-emptying some of the nutrients. Whatever hypothesis is adopted, it should take into consideration the histologic changes in the intestinal epithelium found in these cases. The malabsorption is reasonably considered a secondary effect of epithelial injury.

President Eisenhower's Operation for Regional Enteritis: A Footnote to History is contributed by Leonard D. Heaton, Isidor S. Ravdin, Brian Blades and Thomas J. Whelan.[6]

President Eisenhower, age 65, was taken ill with ill-defined lower abdominal discomfort at 12:30 A.M., June 8, 1956. Examination revealed moderate distention and tympany. By 6 A.M., the pains had become colicky and centered about the umbilicus. Enemas gave no relief. At 10:30 A.M., the patient vomited 1,500 cc. of bile-stained fluid. Examination revealed signs of impending shock, and the hemoglobin value was 21 Gm./100 ml. Parenteral fluids were given, shocklike symptoms disappeared, and the patient was moved to the Walter Reed General Hospital at 1:30 P.M. Examination there revealed diffuse abdominal tenderness.

The history revealed that the appendix had been removed in 1923. Subsequently, the patient had had episodic low abdominal pains, and in 1947 a diagnosis of partial small bowel obstruction was entertained. Nine months before admission, he had had a myocardial infarction One month before admission, a small bowel series

Fig. 52. Small bowel series showing localized regional enteritis in the terminal ileum beneath arrows are seen. (Courtesy of Heaton, L. D., *et al.* Ann. Surg. 159 691-699, May, 1964.)

6. Ann. Surg. 159 691-699, May, 1964

had been performed because of recurrent low abdominal pain and had revealed a picture typical of regional enteritis involving the distal part of the ileum (Fig. 63)

Because of the past history, the presenting findings and x-ray evidence of dilated jejunal loops, a diagnosis of intestinal obstruction secondary to regional enteritis was made, and operation was undertaken at 2 57 A M , June 9, 1956 Dense adhesions were found in the abdomen Typical dry regional enteritis involved the terminal 30-40 cm. of the ileum No skip areas were noted Proximal to the involved gut, intestinal loops were dilated Ileotransverse colostomy was performed, and the operation was concluded at 4 51 A M

The patient's course throughout the operation and postoperatively was satisfactory, although there was some concern about postoperative ileus However, he passed flatus on the 5th postoperative day and took solid food on the 7th day He transacted official business on the 5th postoperative day and was discharged on the 21st day

The decision to operate under the circumstances of the President's illness cannot be challenged, but there has been some question about use of an ileotransverse colostomy. The reasons for use of this procedure are: (1) operation was carried out primarily to relieve obstruction; (2) the enteritis was of the dry, burned-out type, not likely to recur or progress; (3) because the operation was performed as an emergency procedure, the preparation needed for resection was not possible; and (4) if the ileum had been transected and closed, the distal ileal loop might either have blown out or might have required construction of an ileal fistula. The nature of the procedure carried out has been justified by subsequent events. Follow-up x-rays in May, 1963, show that the regional enteritis in the terminal ileum is unchanged except for further cicatrization and that no skip areas have appeared.

► [This is a revealing account, not only of the former President and the skillful care he received, but also of the men who administered that care One would think that the facts would speak for themselves, but astoundingly these four prominent physicians feel that they still have to defend themselves against the criticism leveled at the type of operation they performed, and hence this major historic description ends with the anticlimactic, personal proclamation "We have never wavered in our belief that time would justify the decision made during those fateful hours "—Ed]

Small Bowel Ulceration Apparently Associated with Thiazide and Potassium Therapy. During a 15-month period from June 1, 1963, through August 31, 1964, Daniel R. Baker, Wayne H. Schrader and Claude R. Hitchcock[7] (Hennepin County Gen'l Hosp., Minneapolis) saw 12 patients with ulcerating, predominantly stenosing and obstructing lesions of the small intestine. This was most unusual, since

(7) J A M A 190 586-590, Nov 16, 1964.

benign small bowel ulcers are relatively rare, only about 170 cases having been reported in the world literature.

The ages of the 12 patients ranged from 37 to 86, and in 11, the presenting clinical picture was that of small bowel obstruction. Two had perforation, and 1 had had a recent hemorrhage into the gut Only 4 had undergone previous abdominal surgery. All had cardiovascular disease of varying degrees, and 11 had been receiving enteric-coated preparations of potassium chloride either in combination with or supplementary to hydrochlorothiazide therapy Treatment with these agents had varied from 8 days to 33 months.

Eleven patients were operated on; the other died before surgery could be performed Segmental resection of the involved area was done in most cases The responsible lesions, 5 of which were in the distal jejunum and the remainder in the ileum, varied from 8 to 25 mm in length and were circumferential (Fig. 64) Except in 1 patient, they were solitary. In most instances, stenosis was evident but external constricting bands were found On the mucosal surface, sharp, punched-out ulcers were seen In 1 of 3 patients with a perforation, an undigested enteric-coated potassium tablet

Fig. 64.—Lesion in distal jejunum with marked stenosis and sharp demarcation of ulceration. (Courtesy of Baker, D. R., *et al* J.A.M.A. 190:586-590, Nov 16 1964.)

was found at the site of perforation. In another, 2 undigested ferrous gluconate tablets were found near the perforation, but the patient had been taking these medications for only 2 days. Histologic examination revealed acute and chronic inflammatory ulcers with fibrosis in the submucosa under the ulcer and thickening of the bowel wall. No vascular lesions were seen.

No recognized specific causes for the ulcers could be identified; there was no evidence of syphilis, tuberculosis, neoplasm, vascular insufficiency, or excessive gastric secretion. Digitalis was being taken by only 5 of the patients and iron preparations by 2. Thus, enteric-coated potassium chloride appeared to be the one common factor. The etiologic role of this agent must be considered speculative, but the irritant properties of concentrated potassium chloride solutions on living tissues are well known.

► [The first report on this new clinical entity apparently appeared in the Scandinavian literature (Lindholmer, Nyman and Raf, Acta chir scandinav 128 310, 1964) This, and the first American report presented above, have precipitated a torrent of identification of similar ulcers, and registries have been formed to document the incidence of these ulcers and the circumstances under which they appear (J A M A 191 641, 1965) The etiologic role of potassium, strongly suspected on the basis of circumstantial evidence, seems supported by the studies reported in the following article – Ed]

Experimental Evaluation of Thiazides and Potassium as Cause of Small Bowel Ulcer. In the patients with solitary circumferential small bowel ulcers seen by Scott J. Boley, Leon Schultz, Harvey Krieger, Solomon Schwartz, Alberto Elguezabal and Arthur C. Allen[8] (Jewish Hosp., Brooklyn), 3 aspects seemed worthy of note· (1) Most had microscopic abnormalities in veins and arteries and in the mesentery near the ulcers; (2) most had an underlying cardiovascular condition; and (3) most were taking enteric-coated thiazides with potassium, especially the latter. To determine the role of such therapeutic agents, enteric-coated placebos, enteric-coated potassium chloride, various enteric-coated thiazide-potassium preparations, and thiazides were fixed in segments of distal jejunum or ileum of dogs. The animals were killed 1 or 2 weeks postoperatively except when perforation dictated earlier examination. Gross and microscopic examinations were carried out on all tissue within 4 cm. of a tablet site.

No lesions were seen after dog intestine was exposed to

(8) J.A.M.A. 192:763-768, May 31, 1965

placebos or thiazides alone. Intestine exposed to potassium chloride was either normal or demonstrated a variety of lesions ranging from sharply limited, annular, bluish ridges with intact mucosa to deep circumferential ulcerations, occasionally complicated by perforation or gross infarction. These lesions were invariably 2-3 cm. distal to the area of direct contact with the tablets, apparently in that segment where maximum absorption of the drugs occurred. No predominance of lesions was found in ileum versus jejunum. In general, the marked variation in response to enteric-coated potassium was striking. Thiazide-potassium combinations produced similar but less striking changes.

Important findings on histologic examination were conspicuous submucosal edema, hemorrhage and fibrosis with relatively small degrees of mucosal erosion or ulceration. In addition, phlebosclerosis, intimal edema and sclerosis of arteries was frequently noted. The least severe lesions took the form of submucosal telangiectasia beneath an intact mucosa, without accompanying submucosal edema. In the more severe lesion, the entire wall was hemorrhagic. The walls of intramural vessels frequently showed partial to complete fibrinoid necrosis

Although these studies have obvious artificial components, it is striking that potassium chloride was the specific agent which seemed responsible for the lesions. It would appear that the precipitating cause is a rapid localized release and absorption of potassium chloride, leading to venous spasm, venous stasis, submucosal edema and subsequent ulceration. In man, this vascular response may be aggravated by the underlying vascular disease that most of the patients have. Because of varying individual susceptibility, however, there need not be any relation to dosage of potassium chloride or to duration of exposure.

An important ancillary result of these studies is that thiazides produced no damage whatsoever, and there need not be any limitation to the use of these agents alone.

Carcinoid Spectrum is the subject of an editorial by Albert Sjoerdsma and Kenneth L. Melmon[9] (Nat'l Inst. of Health). Since recognition of the carcinoid syndrome a decade ago, it has become necessary to revise and extend earlier concepts. For example, discrepancies have been noted between the

[9] Gastroenterology 47 104 (Jul. July, 1964.

amount of serotonin produced by the tumor and the severity of the symptoms. This is explained by the fact that pharmacologically active substances other than serotonin are also produced by these tumors. Thus, some patients have the syndrome in the absence of elevated urinary 5-hydroxyindolacetic acid levels, and the characteristic flush may be more easily precipitated by injection of norepinephrine than by injections of serotonin

Some other humoral agents that may be involved are histamine and catecholamines, urinary excretion of these substances having been marked in some patients Other possible mediators are the kinin peptides or kallidins, such as bradykinin, which are highly active substances that produce bronchoconstriction, vasodilation and stimulation of the intestine. These are normally present in glandular structures such as the pancreas and salivary and sweat glands. Peptides of this type have been found to be elevated in the hepatic venous blood of carcinoid patients during epinephrine-induced flushes, and the enzyme kallekrein, capable of producing a peptide from the plasma α_2-globulin kallidinogen, has been isolated from metastatic tumors of several patients. Such vasoactive peptides may well be involved in flush production and possibly in other manifestations of the syndrome.

Other variants of what may be called the carcinoid spectrum appear to be caused by tumors that are not primary in the small intestine. Such extraintestinal sites include the bile ducts, pancreas, ovaries and bronchi. In some of these variant syndromes, tumors have been shown to secrete not serotonin but histamine or 5-hydroxytryptophan. Flushing may be the predominant symptom and diarrhea may be minimal. The most striking variants are produced by bronchial carcinoids, again attended by striking attacks of flushing. Heart lesions may also be found in this type of case but tend to involve the mitral and aortic, rather than the tricuspid and pulmonic valves that are involved in the classic syndrome. The bronchial tumors are frequently associated with pluriglandular adenomatosis. Possibly an extreme variant is a non-beta islet cell adenoma of the pancreas associated with flushing and diarrhea but without evidence of serotonin production.

In the therapy of these conditions, antineoplastic drugs

have yielded no consistently promising results. Agents such as norepinephrine may produce paradoxical hypotension in the carcinoid patient. In some patients chlorpromazine may be useful, and its antibradykinin properties may help alleviate flushing. Attempts to inhibit serotonin synthesis have been only moderately successful, the decarboxylase inhibitor methyldopa (Aldomet) benefiting only a small percentage of patients Perhaps the most useful agents have been antiserotonin compounds such as cyproheptidine (Periactin) and methysergide (Sansert)

Treatment of Malabsorption and Diarrhea of Carcinoid Syndrome with Methysergide was found to be helpful by Kenneth L. Melmon, Albert Sjoerdsma, John A. Oates and Leonard Laster[1] (Nat'l Inst. of Health). The 7 patients studied had typical manifestations of carcinoid syndrome. Two also had steatorrhea. Of these, 1 had had two intestinal resections, involving a segment of ileum and the ileocecal area, respectively. On a daily fat intake of about 100 Gm., she excreted 60-90 Gm. fecal fat per day. The serum carotenoid concentration was reduced to 10 μg./100 ml., and xylose absorption was impaired. Urinary excretion of 5-hydroxyindolacetic acid was 200 mg. per day (normal 2-9 mg.). When she was given a maximal dose of the serotonin antagonist methysergide (one-methyl-D-lysergic acid (+)-butanolamide bimaleate), fecal fat output dropped to below 10 Gm. per day over a period of about 2 weeks, and both the number of the stools and their weight decreased appreciably. On replacement of methysergide with a placebo, the stool abnormalities returned but were again alleviated when methysergide was reinstituted. During these therapeutic trials, no significant weight change took place, but during 6 months after the study she gained 7 kg. while on 12 mg. methysergide daily.

A second patient who had fecal fat excretion ranging from 9 to 30 8 Gm. a day, and who also had had an ileocecal resection, responded less strikingly to methysergide. However, there was some reduction in fecal fat, and prolonged administration of methysergide, 6-10 mg per day, resulted in a 4-kg weight gain over a 7-month period.

Methysergide given in doses of 8-12 mg. per day for 7-28 days to 5 patients with hepatic carcinoid metastases and with diarrhea but no malabsorption produced some subjec-

[1] Gastroenterology 48 18-24, January, 1965

tive and objective improvement in the gastrointestinal symptoms of 4. It even appeared that methysergide was more effective than deodorized tincture of opium in decreasing the daily number of stools. The 1 patient who did not respond to the drug was the only 1 who showed an adverse side effect, and this consisted of lightheadedness and dizziness

► [Although this is an encouraging report, one is also struck by the fact that here is another agent, pharmacologically a good serotonin antagonist, which under clinical circumstances is only partially successful in alleviating symptoms supposedly produced by serotonin Perhaps, as was pointed out in the previous abstract, agents other than serotonin itself are responsible for many of the clinical phenomena of the carcinoid syndrome

Methysergide has been implicated as a possible cause of retroperitoneal fibrosis (J A M A 191 983, 1965), but this potential complication should hardly prevent use of the drug in a condition as serious as the carcinoid syndrome —Ed]

Complete Reflux Small Bowel Examination is advocated by Roscoe E. Miller[2] (Indiana Univ.) as a new method which will not completely replace others but does offer fast and accurate diagnosis of small bowel lesions in a great number of cases.

METHOD —In emergency cases or in patients with suspected bowel obstruction, no preparation is used. Otherwise, the patient is given 2 oz castor oil as in usual preparation for barium enema examination. A 20% w/v suspension of specially prepared barium which does not flocculate or precipitate is used, and the suspension is administered through large-bore tubing (internal diameter, 3/8 in) and a tip provided with an inflatable cuff that prevents evacuation until desired. The colon is filled in the usual manner, usually requiring about 1,500-2,000 cc. of suspension, and x-rays are taken

The patient is then turned on his back, and barium is again allowed to flow under fluoroscopic control until it is observed in the duodenal bulb. Alternatively, 2,000 cc. of near-normal saline solution is substituted for the last 2,000 cc of barium suspension after reflux into the terminal ileum has been initiated This reduces the amount of barium in the colon and minimizes superimposition of large and small bowel loops Once barium has reached the duodenum, or a total volume limit of 4,500 cc , one prone film is taken, the patient is returned to the supine position, and the barium is rapidly drained from the bowel After drainage, fluoroscopy is again performed, with a search for stenotic or other small bowel lesions. More films are taken, the patient is sent to the toilet for a 15-30 second evacuation, and the final set of films are exposed The whole procedure usually takes 15-20 minutes.

Inability to overcome the ileocecal valve is a rare cause of failure and has occurred only three times in over 75 cases. Usually, the enema reservoir does not have to be more than 3 ft. above the table top, but occasionally it has been raised an

(2) Radiology 84 457-463, March, 1965

additional 4 in. to achieve reflux into the small intestine. The examination is painful, but no more so than other common diagnostic procedures such as esophagoscopy and cystoscopy. One of the first reflux small bowel examinations was performed on the author himself: it was discovered that the patient's gown must be loose because of the considerable abdominal distention that develops Because of the patient's discomfort, the radiologist who is inexperienced makes the common mistake of not waiting long enough for the duodenum to fill. Drugs to relieve pain or affect motility have not been injected, although others have given atropine and calcium gluconate, partly to overcome the barrier of the ileocecal valve. Occasionally, especially if there is a redundant large bowel, adequate examination is prevented by superimposition of bowel loops, but if the enema device provides for rapid drainage, this source of difficulty can usually be obviated. No complications have been encountered, but a possible hazard is administration of too much barium, which could result in massive aspiration.

Complete reflux small bowel examination is not advocated for study of derangements of small bowel physiology, such as may be found in sprue. It is recommended for patients with acute small bowel obstruction and for those with abdominal pain and diarrhea in whom a partial obstructive or constrictive lesion of the small bowel is possible. In these, it offers the tremendous advantage that the entire small bowel may be rapidly visualized under fluoroscopic control with ready identification of the site and nature of any possible obstructing lesion During the reflux small bowel examinations, no reverse peristalsis is seen The small bowel and eventually the stomach simply fill in a retrograde manner

► [Are this method's advantages sufficiently great to offset the pain it may engender? In the case of lesions that completely or partially obstruct the small bowel, particularly its lower portions, the answer may well be "yes," but some of the author's comments strike the reader as not only unconsciously humorous but also somewhat alarming, to wit, "the most common mistake made by the beginner is failure to wait long enough for the duodenum to fill because of patient discomfort." And "it was noted that the patient's gown should be loose because of considerable abdominal distention A tightly tied gown can be quite distressing." And "barium should not be allowed to flow unattended, as too much barium could result in massive aspiration."

Some of the great advantages of the ordinary small bowel x-ray examination is that it does *not* cause as much discomfort as esophagoscopy and cystoscopy, that it is esthetically acceptable even if the taste is unappealing and that it may be ordered repeatedly A factor of considerable importance, but one not mentioned by Miller, is the relative amount of radiation exposure required by

his technic and by conventional methods of small bowel x ray examination – Ld]

Hybaroxic Treatment of Experimental Intestinal Obstruction. Absorption of air from an obstructed bowel loop can be increased if the blood nitrogen content is decreased, thus increasing the lumen-blood nitrogen gradient and promoting diffusion of this gas out of the loop. The blood nitrogen content can be decreased by inhalation of nonnitrogen-containing gas, such as 100% oxygen. Frederick S. Cross[3] (St. Luke's Hosp., Cleveland) studied the effect of varying gas pressures on this phenomenon

Obstructed small bowel loops were made by ligation in lightly anesthetized dogs; 150 ml. air were injected into each loop; and the dogs were then exposed to several gas mixtures at normal atmospheric pressure or at pressures of up to 4 atmospheres in a compression chamber. At the end of each test, the dogs were re-anesthetized, residual gas in the obstructed loops was aspirated, and the per cent absorption was determined.

When the dogs inhaled ordinary air at 1 atmosphere pressure, about 11% of air diffused from the obstructed loops during 6 hours. Under 2 atmospheres pressure, 27% left the loop, and under 3 and 4 atmospheres, 34 and 41% respectively, disappeared. In dogs maintained under 2-4 atmospheres, the tone and viability of the bowel were remarkably well preserved even for periods as long as 24-92 hours, presumably because the volume of gas in the obstructed loop had been reduced in direct inverse proportion to the pressure. Impaired viability was evident in only 6 of 60 dogs exposed to high pressures, as opposed to atony and gangrene of obstructed loops in 19 of 27 dogs exposed to normal atmospheric pressure. The increased viability of the loops kept under high pressures probably accounted for the increased absorption of gas from these loops.

When the inhaled mixture contained 95% oxygen and 5% nitrogen, absorption from the closed loops after 6 hours was 38% at 1 atmosphere and 45% under 2 atmospheres. After 12 hours, the corresponding figures were 47 and 63%. Thus increased pressures enhanced the beneficial effect of administering a gas with a low-nitrogen content. However, all dogs breathing 95% oxygen at 2 atmospheres for 12 hours had signs of oxygen intoxication consisting of restlessness, dysp-

(3) Dis Chest 47 374 381, April, 1965

nea, loss of consciousness and rigidity of limbs. Pathologic examination of the oxygen-intoxicated dogs showed pulmonary edema and consolidation. Optimal diffusion with minimal oxygen intoxication was obtained by giving 95% oxygen under 2 atmospheres pressure for 6 hours.

Use of oxygen-helium mixtures in ratios of 80:20 and 60:40 did not significantly improve the results obtained over those obtained when air was inhaled, for as nitrogen was absorbed from the loops, helium diffused into them.

The increased viability of closed intestinal loops exposed to hyperbaric conditions suggests that this procedure, as well as administering gas of low-nitrogen content, should prove beneficial in treating patients with bowel obstruction, and preliminary findings of O. H. Wangensteen indicate that good results are obtained.

► [As long as nonnitrogen-containing gas is inhaled, there is no reason, based on purely physical principles, why the diffusion of nitrogen from obstructed bowel loops containing air should be enhanced by hyperbaric conditions The beneficial effects must thus be attributed to the reduced volume of gas, whatever its composition, in bowel loops kept under high pressure, with consequent improvement in blood flow and tissue viability If the converse holds, and doubling of gas volume at ½ atmosphere of pressure is correspondingly deleterious, the incidence of gastrointestinal complaints in our air- and space-traveling public may well increase —Ed]

Crohn's Disease of the Large Intestine. The clinical and pathologic features of this disease, as seen in a series of 75 patients, are described by H E. Lockhart-Mummery and B. C. Morson[4] (St. Mark's Hosp., London). Sex incidence was equal. Although incidence was highest in the 2d and 3d decades, a higher proportion of the patients were middle aged or elderly than has been reported in Crohn's disease of the ileum. The clinical features are shown in Tables 1 and 2. Severe toxicity and toxic dilatation of the colon, such as occur in ulcerative colitis, were not seen.

Twenty patients had diffuse involvement of most of the

TABLE 1 – PERCENTAGE INCIDENCE OF CLINICAL FEATURES

Diarrhea	88
Anal lesions	81
Loss of weight	65
Abdominal pain	45
Rectal bleeding	45
Anemia	20
Palpable mass	8
Malaise and weakness	15

TABLE 2 —First Symptoms (%)

Diarrhea	52
Anal lesions	27
Abdominal pain	13
Rectal bleeding	5

large bowel with disease of terminal ileum, 21 had diffuse involvement of large bowel without ileal disease, 18 had single segments of large bowel involved, 9 had multiple diseased segments separated by normal intestine, 11 had involvement confined to sigmoid, rectum and anal canal and in 5 the distribution was unknown. In about 30% of the entire group the ileum was involved and in about 50% the rectum. In 3 of those with gross evidence of disease limited to the distal colon, microscopic examination showed the appendix to be affected

Anal lesions were found in 80%, and the incidence was not affected by the distribution of the disease in the colon or ileum. Among 100 patients with ulcerative colitis, by contrast, anal lesions were found in 23. In some patients, the anal lesion in Crohn's disease displayed multiple fissures with an undermined appearance. In others anal fistulas were prominent, but the most characteristic finding was an indolent ulceration extending from the anal verge outward and also up the anal canal Biopsy revealed a sarcoid reaction in 25 of 29 specimens of anal tissue.

In 20 of the 75 patients an anal abnormality was the first manifestation of the disease, and in 7 it was the dominant feature. Severe pain was rare. In most patients the anal lesion remained active until the large bowel disease had been excised surgically, and even then local surgery was sometimes necessary before complete healing was achieved. In a few patients the lesions healed spontaneously.

Sigmoidoscopy in those in whom the disease was in the more proximal bowel showed normal mucosa. In those with rectal involvement the mucosa was congested, with a cobblestone appearance. Often the involvement was patchy, with islands of normal intervening mucosa. The findings were quite different from those seen in ulcerative colitis. Biopsies of ulcerated or nodular areas showed sarcoid foci in 16 of 19 cases (Fig. 65).

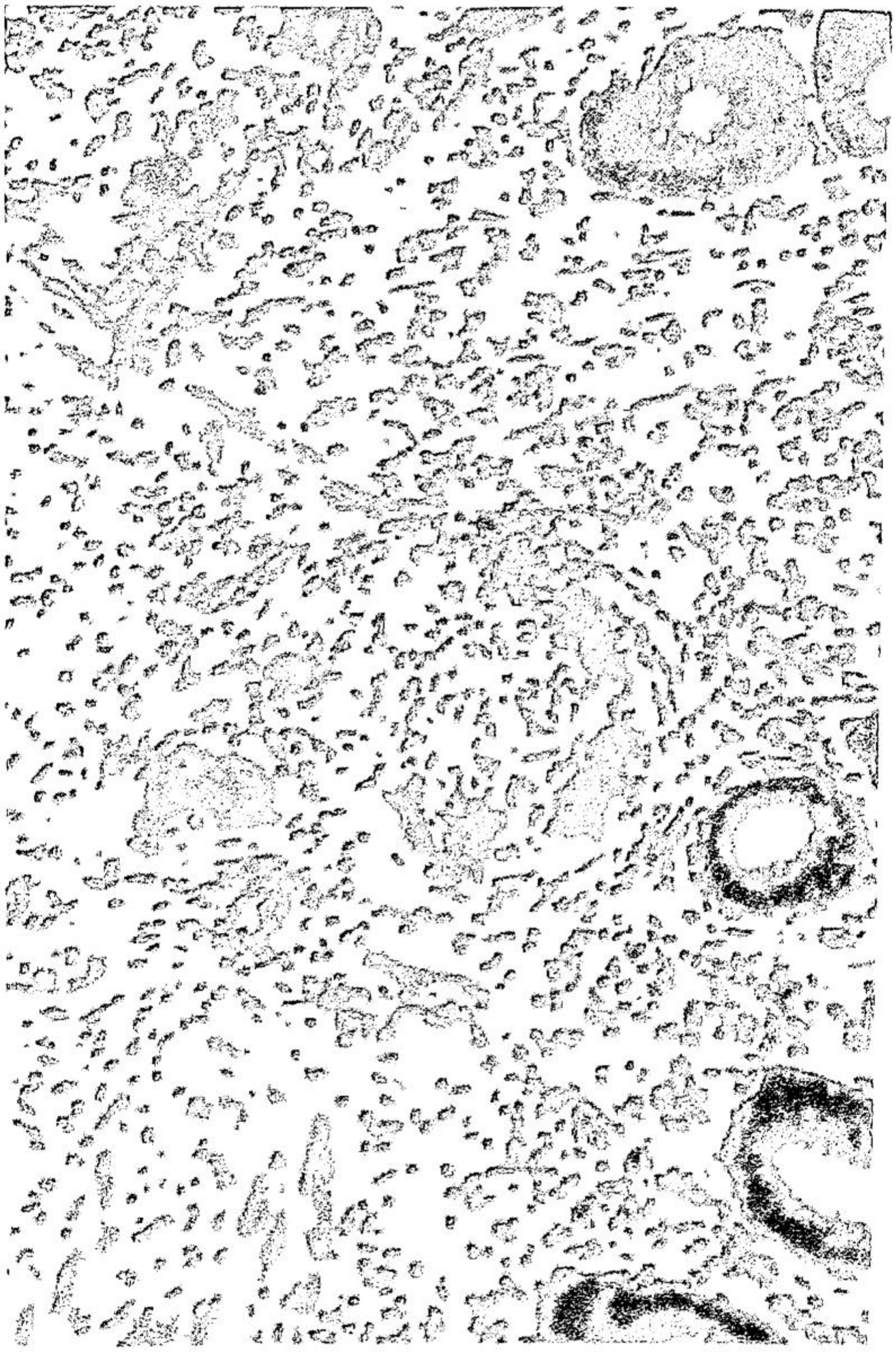


Fig. 15. Rectal biopsy specimen showing foci of sarcoid tissue in lamina propria of mucosa. (Reproduced from Counsell, J. N., Lockhart-Mummery, H. J., and Morson, B. C. Gut 5 493 (6) December, 1964.)

Six patients had spontaneous fistulas—colocolic, duodenocolic or enterocolic. Such lesions never occur in patients with ulcerative colitis. Four had rectovaginal fistulas. An occasional feature was severe and extensive skin ulceration, usually spreading from an area of surgery, where an ileostomy had been fashioned or a rectum excised.

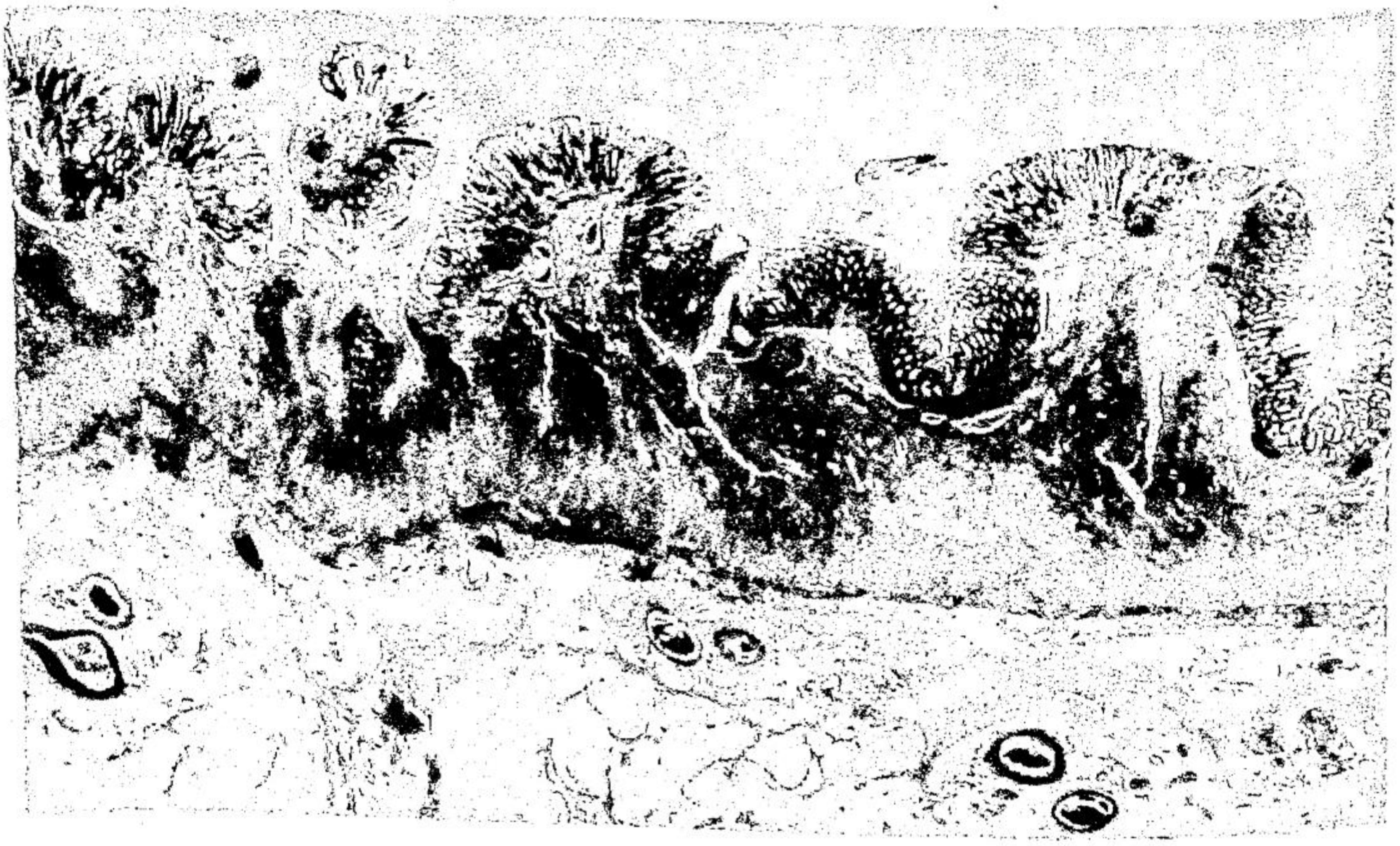
Examination of surgical specimens showed that the mucosal surface of the colon in Crohn's disease had the same cobblestone appearance characteristic of this disease in the small bowel. Between the nodularities, crevices (actually

linear ulcers) could be seen extending into the gut wall Lymph nodes were not invariably enlarged, and correlation between their size and the presence of a sarcoid reaction was poor. This reaction was found in 87% of colon specimens removed surgically, but this high incidence also reflects careful examination of multiple sections. Ten per cent of those with a sarcoid reaction had Schaumann bodies.

Although the sarcoid reaction was the most reliable diagnostic feature, its presence was not essential to histologic diagnosis In the absence of a sarcoid reaction, the most valuable diagnostic feature was the presence of "fissures," or microscopic sinuses, passing from the ulcerated mucosal surface deep into the bowel wall and sometimes beyond into the peri-intestinal tissues (Fig. 66). These crevices were lined by granulation tissue and inflammatory cells and were found, in this series, in 25% of specimens.

Crohn's disease of the colon has not been sufficiently recognized, but the total clinical, radiologic and pathologic picture is such that it should be readily differentiated from ulcerative colitis, which is rarely, if ever, associated with Crohn's disease. Besides ulcerative colitis, differential diag-

Fig 66 Crohn's disease of large intestine, with "fissures" or linear ulcers passing from mucosal surface deep into bowel wall Most of mucous membrane is intact but raised by underlying inflammation, accounting for typical macroscopic cobblestone appearance ×15 (Courtesy of Lockhart Mummery, H E and Morson, B C Gut 5 493 508, December 1964)



nosis includes tuberculosis, diverticulitis and, occasionally, carcinoma.

► [This article supports the thesis propounded last year by a group from New York's Mt Sinai Hospital (see the 1964-65 YEAR BOOK, p 579) in a study that emphasized the radiologic features of what was called granulomatous colitis The English authors prefer the eponym Crohn's disease, as they feel granulomatous colitis is too nonspecific. Rumor has it, however, that at the Mount Sinai Hospital, any eponymic designation would have to be "Crohn-Ginzburg-Oppenheimer disease"—just to keep everybody happy—and that this is considered too much of a mouthful In any case, both groups argue that regional enteritis involving the colon should be and can be differentiated from ulcerative colitis

The attitude taken by Lockhart-Mummery and Morson is quite dogmatic As a result, their article is topflight teaching material, and it deserves special praise for the emphasis it places on the frequency of anal lesions in regional enteritis whether of the large or small bowel On the other hand, their insistence that ulcerative colitis and regional enteritis of the colon are clearly different with respect to incidence, clinical characteristics and pathologic findings is neither consistent with the experience of others nor with what we know about these diseases in general After all, no one knows for sure that ulcerative colitis and regional enteritis each represent an etiologic entity Perhaps there are two or more etiologies which may lead to a process which we call ulcerative colitis, and the same holds true for the disease described by Crohn, Ginzburg and Oppenheimer Hence, it seems unlikely that a sharp line of distinction can always be drawn between the two processes, even though they usually manifest quite typical characteristics —Ed]

Prednisone as Maintenance Treatment for Ulcerative Colitis in Remission was tested by J. E. Lennard-Jones, J. J. Misiewicz, A. M. Connell, J. H. Baron and F. Avery Jones[5] (St. Mark's Hosp., London) Cortisone had previously been shown to be effective in relieving acute attacks of ulcerative colitis, but 50 mg. daily did not appear to prevent relapses. Consequently, a relatively larger dose of prednisone, 15 mg. daily, was tested as maintenance treatment and compared with the effects of a placebo.

Patients took part in the trial when an acute attack had been successfully treated with corticosteroids and when the dose of steroid could be reduced to 15 mg. prednisone or less. Those receiving the placebo were given small doses of prednisone during the first 2 weeks of the trial to avoid abrupt withdrawal of the steroid The 32 patients receiving prednisone and the 30 receiving placebo (allocation to groups was on a random basis) were comparable with respect to age, sex and distribution of the disease in the colon. Patients were seen 2 weeks after start of the trial and thereafter at intervals of 4 weeks for 6 months, if no relapses occurred in the

[5] Lancet 1:188 189, Jan. 23, 1965

meantime. The physicians were unaware of the nature of the medication taken by the patients.

In both groups, 12 patients remained in remission for 6 months, but 18 who received prednisone and 17 who received the control tablet relapsed within this time. Side effects appeared in 9 patients, 7 of whom were receiving prednisone and 2 the placebo. Prednisone, 5 mg. 3 times daily, does not appear to be effective in preventing relapses of ulcerative colitis.

► [This list of authors is practically a "Who's Who" of British gastroenterology, and the combined weight of their results and their authority is certainly discouraging for those who would use maintenance doses of steroids in an attempt to prevent relapses Actually, good theoretical reasons exist for not using long-term steroid maintenance treatment for ulcerative colitis in remission The danger of side effects is too real, and the management of a relapse, should one occur, is extremely difficult, as one may have to choose between massive doses of steroids and surgery in treating a patient who is steroid-dependent, infection-prone and osteoporotic —Ed]

Controlled Trial of Sulphasalazine in Maintenance Therapy for Ulcerative Colitis. Since 4 of 5 patients who respond to medical treatment of a first attack of ulcerative colitis have a second attack within 12 months, J. J. Misiewicz, J. E Lennard-Jones, A. M. Connell, J. H. Baron and F. Avery Jones[6] (St. Mark's Hosp., London) compared the efficacy of Azulfidine (0.5 Gm. 4 times daily) and a placebo in preventing relapses of proctocolitis

Outpatients who had had an attack of proctocolitis in the previous year and who had no history of intolerance to Azulfidine were assigned to two groups on a random basis, 34 patients receiving Azulfidine and 33 a placebo tablet. The groups were comparable with respect to age and sex, but distribution of the disease differed to a mild degree in that extensive involvement of the colon was found in 3 patients in the Azulfidine group and in 5 in the placebo group. The patients were examined by physicians unaware of the medication being taken at 2, 4, 6, 9 and 12 months after treatment was begun. The status of the patient was determined on the basis of symptoms and sigmoidoscopy.

Of the patients taking Azulfidine, 24 remained asymptomatic, compared with only 8 in the placebo group. On a statistical basis, this difference was strikingly significant. Most relapses in both groups took place within 4 months after start of the trial. Three patients in the Azulfidine group and 1 in the placebo group stopped treatment because of

(6) Lancet 1 185 188, Jan 23, 1965

nausea and abdominal pain. No important changes in hemoglobin values or white cell counts were observed in those taking either preparation. A relatively small dose of Azulfidine (2 Gm. daily) appears to be effective in reducing the relapse rate in ulcerative colitis.

► [In view of the results obtained in this study and those obtained when steroids were used as maintenance therapy (see preceding article), the authors conclude that Azulfidine is preferable to steroids for the purpose of preventing relapses in ulcerative colitis. The difficulty with their Azulfidine study is that no indication is given as to whether or not the patients had had steroids before. Thus, in the steroid study, patients previously treated with these agents were necessarily tested, whereas one would suspect that Azulfidine was used in patients who either had not had steroids previously or who had not taken these agents for some time. In addition, the Azulfidine-treated patients were outpatients who may have had a milder disease than those who received the steroid maintenance trial. It would be interesting to know how Azulfidine would work as maintenance therapy in patients who had been so ill with ulcerative colitis as to require steroid therapy.

These objections, however, in no way controvert the most impressive effects that Azulfidine apparently may have in patients with moderate ulcerative colitis limited to the distal colon.

Dick and his associates report in a double-blind study that Azulfidine appeared beneficial in about three fourths of patients with mild to moderate ulcerative colitis treated with this agent (Gut 5:437, 1964), but on a dose that usually ranged from 4 to 6 Gm. daily, nearly 40% of patients taking the drug experienced nausea, vomiting, anorexia, indigestion, heartburn or abdominal discomfort.—Ed.]

Intraluminal Pressure Patterns in Diverticulosis of the Colon.—I. *Resting patterns of pressure* were measured by Neil Stamford Painter and S. C. Truelove[7] (Radcliffe Infirm., Oxford, England) in control subjects and patients with diverticulosis. Three water-filled, open-ended tubes were inserted into the sigmoid; the openings of the tubes were 7.5 cm. apart. Records were obtained for 1 hour while the patient was resting in a basal state. The control subjects and patients with diverticulosis did not match with respect to age, but in the control group there was no difference noted in the motility records obtained from patients in various age groups.

In the normal sigmoid, a steady base-line pressure was recorded; superimposed on this was an irregular pattern of pressure waves, which sometimes occurred singly and sometimes in series. Pressure waves at one level of the sigmoid often occurred independently of the pressure at another level, and there was usually no strict temporal relationship between waves recorded in the three leads. Except when flatus was passed, the records showed no evidence of progression of a pocket of high pressure toward the anus. On

7. Gut 5:961-967, June, 1964.

the whole, considerable variation in the pattern of waves recorded was evident, not only between different subjects, but in the same subject when tests were performed on different days.

Two types of waves were predominantly seen. The first showed a gentle rise of pressure to a height of less than 10 mm. Hg with an equally gentle decline; these waves lasted between 10 and 30 seconds. The second type displayed a more rapid rise of pressure, reached a greater amplitude of 10-30 mm. Hg and also had a steeper fall Its duration was 10-40 seconds. Between these two forms, a variety of gradations were seen.

In the patients with diverticulosis, no obvious differences from the tracings obtained in the normal subjects were seen. Even if special attention was paid to records from tips that were located in the immediate vicinity of diverticula, defined as "patterns related to diverticula," no changes separating such records from normal records were recognizable This lack of difference was confirmed by counting the frequency of waves of various amplitude per hour of recording The distribution of pressure waves of various intensity was about the same in normal subjects and in patients with diverticulosis, whether or not the position of the tips was related to diverticula. Calculation of a "motility index" (height of waves × duration × number of waves measured per hour) also revealed no differences Thus, no evidence could be found that patients with diverticulosis have higher intraluminal pressures in the sigmoid under resting conditions than do normal subjects.

II.—*The effect of morphine* on the pressures in the human colon was measured by Painter and Truelove.[8] After intravenous administration of this drug, basal intraluminal pressure rose by a few millimeters and, superimposed on this rise, a succession of high pressure waves was apparent. This burst of activity was followed by a few minutes of inactivity and then by another series of waves. After this initial motor response, a rhythmical succession of small pressure waves appeared intermittently at one or more leads and produced a pattern of alternating activity and inactivity that might persist for most of the recording period.

Pressure waves after morphine arose independently at

(8) Gut 5 207-213, June, 1964

each level of the sigmoid, the recording pens moving asynchronously in almost all instances. The fact that asynchronous waves of different magnitude were recorded from segments of sigmoid separated by only 7.5 cm. suggested that the responsible mechanism was local in origin and that the sigmoid colon can isolate multiple regions of high pressure. Morphine, moreover, appeared to activate the mechanism responsible for producing localized high-pressure pockets.

In patients with diverticulosis, morphine produced pressure tracings similar to those seen in normal subjects when the openings were not immediately in the vicinity of diverticula. When a lead was positioned within a segment bearing diverticula, however, clear differences were apparent. Although each wave was of normal duration, some waves reached exceptional heights, their peaks often exceeding 50 mm. Hg in pressure, and their ascending and descending limbs were correspondingly precipitous. Sometimes up to 20 such large waves occurred in quick succession. Postmorphine waves exceeding 50 mm. Hg in pressure were not seen except in diverticula-related records. The postmorphine motility index showed double its average resting value in normal subjects, treble in nonrelated leads in patients with diverticulosis and a sixfold increase in leads related to diverticula. Whether the increased sensitivity to morphine of sigmoidal areas bearing diverticula precedes or follows formation of these pouches cannot be stated, but in one patient the presence of a single diverticulum was associated with an exaggerated motor response to morphine. It is possible but unproved that other stimuli may cause a similar differential motor response in normal colon and in sigmoid affected by diverticula. Whatever the theoretical implications, it appears that morphine should not be used as an analgesic for treating pain in patients with diverticulosis and diverticulitis.

► (These parts I and II of this article are followed by two other parts (Gut 5:355 and 369, 1964) which essentially state that an effect similar to that of morphine is produced by prostigmine in sigmoidal segments bearing diverticula, that the morphine effect can be abolished by an intravenous injection of Pro-Banthine, and that pethidine (Demerol) does not increase intrasigmoidal pressure. Part V (Gut 6:57, 1965) reports the results of combined manometric and radiologic studies. It provides evidence that during the segmental contractions of the sigmoid which produce the localized zones of high pressure, the necks of diverticula in the segment are not occluded but, to the contrary, are sufficiently patent that intrasegmental pressure could readily be transmitted into the diverticular pouches.

Painter sums up his studies in an article discussing the etiology of diverticu

losis of the colon (Ann Roy Coll Surgeons England 34 98, 1964) Although he admits that his studies do not prove that excess intraluminal pressure causes the diverticula, he allows that the possibility is a good one The concept of localized sigmoidal pockets of high pressure is certainly consistent with Morson's description of thickened rings of circular muscle in the sigmoid with diverticulosis (see the 1964-65 YEAR BOOK, p 593) As a most interesting speculation, Painter suggests that a low-roughage, low-residue diet may lead to progressive contraction of the sigmoid which then develops the capacity to form the necessary high pressure pockets. People who eat more roughage are less apt to have diverticula, as is true, according to Painter, of the West African native, and, according to B O. Urteaga, of the Indian in the South American Andes and, according to Eung Ho Kim, of the natives of Korea (see p 351) The therapeutic implications of these speculations, if they are correct, is clear the practice of treating patients with diverticulosis with a low-residue diet may be more harmful than beneficial!

The recording of intraluminal pressures in both the small and large intestine has been a relatively popular investigational pastime of late, and a spate of publications on this subject has appeared With some exceptions, however, they have not added up to much, for the practical and theoretical problems are considerable No one has yet devised a satisfactory method for measuring motility on the basis of motility records and expressing it in a number that can be used for quantitative purposes For this reason, those that have used intraluminal pressure recordings have gone through the same sequence of ideas pursued by those that 20-30 years ago were measuring gut motility by means of large balloons Indeed, a special convocation was held to organize a standard system of measuring motility (Am J Digest Dis 10 481, 1965), but few suggestions were made beyond the usual practices of measuring numbers of waves, their heights and their surface area or computing a motility index similar to the one used by Painter and Truelove A much more sophisticated approach was made by Small, Brean and Farrar, who attempted to apply autocorrelation and Fourier transformation to the analysis of motility records (J Gen Physiol. 38.695, 1955) but found that the results were no better than those obtained by gross visual inspection or by applying a rather simple type of motility index

The theoretical problems are even greater for those who measure intraluminal pressure than they were for those who used large balloons. The latter, at least, could express their results in terms of local wall squeeze, for when the record from the large balloon showed that its volume was being diminished, one could interpret with considerable confidence that the intestinal wall around the balloon was contracting This is not the case with records of intraluminal pressure, for pressures created within any one segment of gut depend not only on what the local wall in the immediate vicinity of the recording tip is doing, but also on pressures transmitted from above and, even more important, by the resistance offered to the transmission of pressure by areas of gut below and above the recording site This point is well elucidated in a series of studies by Connell and his associates on the motility of the colon (Gut 5·443, 1964 and 6 105, 1965).

Intraluminal pressure records are particularly helpful when used for the study of gastrointestinal areas that tend to form, as part of their normal motor patterns, isolated segments of high pressure, such as the esophagus and, as Painter, Truelove and Connell have shown, the sigmoid colon Even though no really satisfactory system is available for quantitating the intraluminal pressure records obtained from such areas, the patterns are sufficiently distinct to permit reasonably meaningful interpretation. At present, the same cannot be said with any confidence about intraluminal pressure records obtained from the small bowel or proximal colon —Ed]

Retrograde Spread of Contrast Medium Released from Suppositories: Partial Explanation for Efficacy of Therapeutic Suppositories is offered by Julius G. Parker and Stanley Siegelman[9] (Montefiore Hosp., Bronx, N.Y.). Two standard-size cocoa butter suppositories containing 2.5 ml. Gastrografin were inserted into the rectum of each of 31 subjects. Two were tested twice. No preparation was given prior to the study; no laxatives or enemas were taken for 3 days before the study; and no subject had defecated for at least 5 hours preceding the test. After insertion of the suppositories, the subjects remained in one of several positions for 2 hours while x-ray films were taken every 30 minutes.

In all tests, opaque medium was seen in the rectosigmoid area, but in 4 it extended to the sigmoid, in 9 to the mid-descending colon, in 9 to the splenic flexure and in 2 to the hepatic flexure Maximum retrograde flow was usually noted in 1-2 hours, and the position which appeared most favorable for such retrograde flow was the posteroanterior. The opaque material appeared to ascend the colon as much in patients with ulcerative colitis as in those with irritable colon.

In use of rectal suppositories for therapeutic purposes, medications administered in suppositories may be expected to reach the mid-descending colon in about two thirds of instances, but in a few cases, retrograde flow may be inadequate to reach a diseased area above the rectosigmoid.

► [This is a practical little study which is somewhat reminiscent of the experiments quoted by W C Alvarez (*An Introduction to Gastroenterology* New York Paul B Hoeber, Inc], 1940) maintaining that lycopodium spores given by enema could subsequently be found in the stomach This may have been carrying things too far, but the upward spread of rectally inserted medication may apparently be considerable Unfortunately the authors did not check reproducibility in more than two subjects As of the present, therefore, it is uncertain whether the degree of retrograde passage of material inserted by rectal suppository varies from test to test or from individual to individual —Ed]

Contribution of the External Anal Sphincter to the Pressure Zone in the Anal Canal was studied by H L Duthie and J. M. Watts[1] (Gen'l Infirm., Leeds, England) by means of a pressure-recording device equipped at its distal end with either an open tip or a water-filled balloon 5 mm in diameter A larger balloon, 5 × 7 cm., was placed higher up in the rectum to provide intermittent distention. In addition, a

(9) Am. J. Digest. Dis. 10:463-466, May, 1965.
(1) Gut 6:63-68, February, 1965

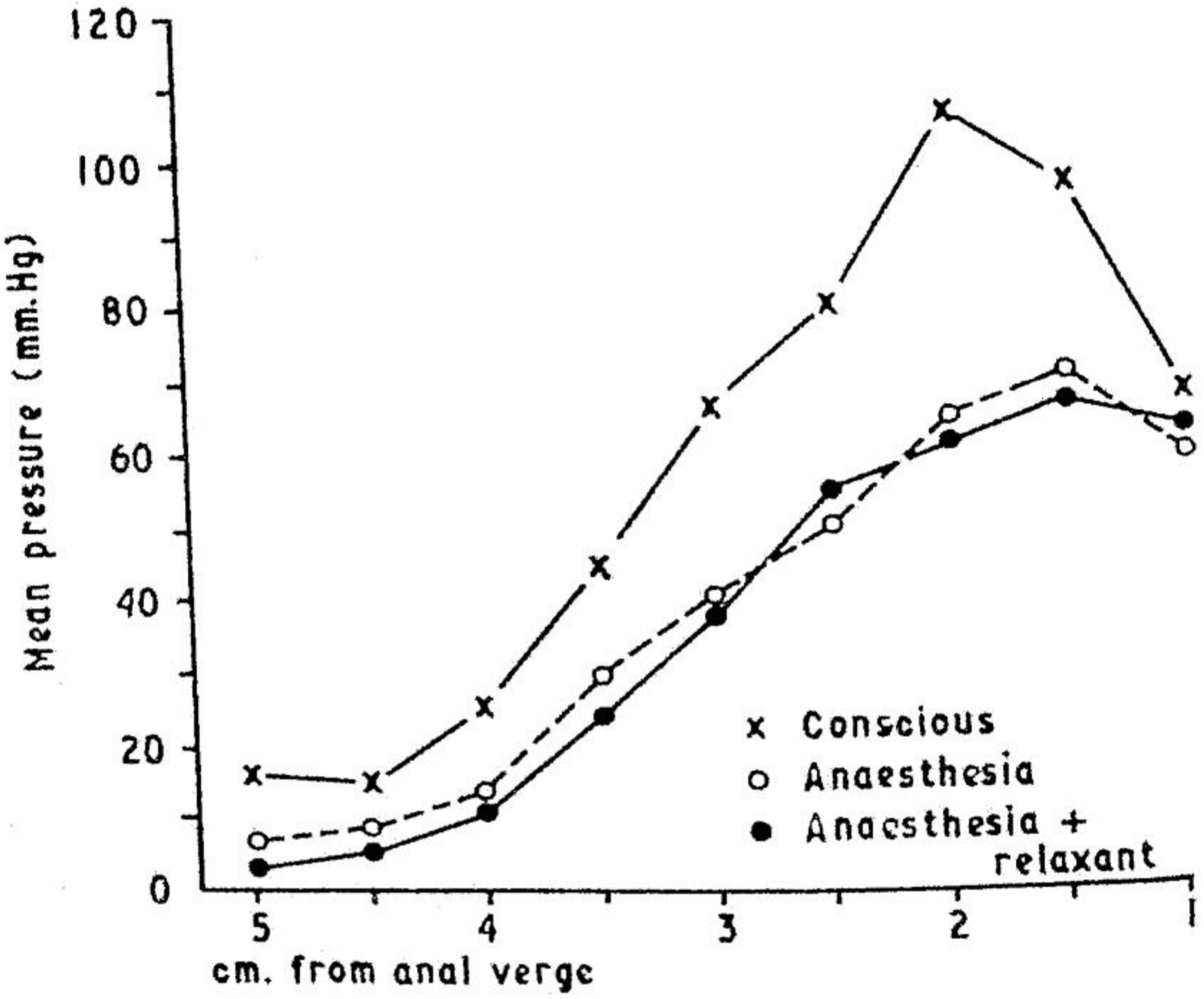


Fig. 67 – Mean pressure in lower rectum and anal canal recorded via a small balloon (5×10 mm.) in 10 subjects when conscious, when anesthetized and when anesthetized and fully paralyzed. Diminution in pressure from the conscious level is significant ($P < 0.01$ at 1.5-4 cm. from the anal verge inclusive. $P < 0.02$ at 4.5 cm. from the anal verge.) (Courtesy of Duthie, H. L., and Watts, J. M., Gut 6:64-68, February, 1965.)

concentric needle electrode was inserted into the external anal sphincter in order to obtain an electromyogram.

Ten subjects were studied at rest, after administration of light anesthesia and finally after administration of a muscle relaxant such as succinylcholine. When the pressure-recording tip was withdrawn in small steps through the anal sphincter, recorded mean pressures gradually rose from 13 mm. Hg at 5 cm. from the anal verge to 37 mm. Hg at 2 cm. from the verge and then dropped to 17 cm. at 1 cm. from the verge. A moderate decrease in this pressure profile, significant at the 5% level at 2 and 3 cm. from the anal verge, was produced when the subjects were examined under light general anesthesia, and subsequent addition of the muscle relaxant did not change this pattern. When the small balloon was used at the recording tip, qualitatively the same pressure profiles were obtained on withdrawing the tip through the anal sphincter, but the mean pressures were higher than with the open tip, e.g., 105 mm. Hg when 2 cm. from the anal verge (Fig. 67); and light anesthesia, with or without additional muscle relaxation, produced a more significant fall in the pressures recorded at all distances from the anal verge.

These findings suggest that the external sphincter does play a role in maintaining intra-anal pressure at rest.

The electromyographic record after anesthesia showed some reduction in magnitude of the spiking potentials, and sometimes the record was blurred and unclear. Thus the electromyogram suggested that light anesthesia did affect external sphincter activity and helped explain the somewhat paradoxical observation that addition of a muscle relaxant to light anesthesia did not affect the intra-anal pressure profile.

If the same tests were carried out during inflation of the large rectal balloon with 100 ml. of air, pressure throughout the anal canal was diminished, and this decrease took place whether or not anesthesia and muscle relaxation had been induced. The rectal myographic pattern was not particularly affected by distending the large rectal balloon except for temporary bursts of activity immediately on its inflation or deflation

Since relaxation after balloon distention took place whether or not anesthesia and muscle relaxants had been given, it seems unlikely that the external sphincter took any part in the well-known relaxation response to rectal distention The failure of the external sphincter to respond to rectal distention was supported by the myographic findings of continuing activity despite the distention stimulus. It is concluded that the internal sphincter must be largely if not wholly responsible for the reflex relaxation of the anal sphincter in response to rectal distention

Three components appear to contribute to pressure in the anal canal: (1) internal sphincter activity, (2) external sphincter activity and (3) a component of unknown source. The external sphincter component, however, is small; it may be that at rest this component does not contribute to anal continence, but comes into play in maintaining continence only when a bolus enters the upper part of the anal canal.

► There has been a considerable reawakening of interest in the anal sphincter. Duthie and his collaborators have used recording apparatus such as described here to record the pressure profile obtained when the recording tip is slowly drawn through the sphincter according to a technic which has been popularized by Code and his associates at the Mayo Clinic. The pressure profile obtained, as indicated by Figure 67, exhibits a clear-cut hump with its apex at a point 2 cm. above the anal verge. On the basis of such pressure patterns, Duthie's group analyzed the functional importance of the internal anal sphincter (Brit. J. Surg. 51 355, 1964) and the relation of sensation in the anal canal to adequate sphincteric function (Gut 4 179, 1963).

A different type of recording apparatus has been used by Schuster, Hendrix and Mendeloff (J Clin Invest 42 196, 1963 Bull Johns Hopkins Hosp 116 79, 1965) These investigators used larger balloons and have, therefore been measuring the degree of wall squeeze, as opposed to the attempts made by Duthie to measure intraluminal pressure

The substance of the following article, however, throws a bombshell into the entire picture The principal target of this bomb is the technic of recording intra-anal pressures, but the implications go far beyond the anal sphincter and raise the possibility that any measurement of pressure within a closed sphincter, whether obtained by open or small balloon-covered tips, yields records containing much and sometimes pure artifact If Harris and Pope's contentions are correct, records such as obtained by Duthie's group have little meaning

At first glance, it would seem impossible to explain the type of pressure profile shown in the illustration in terms of Harris and Pope's views It must be recognized, however, that the points graphed represent averages, and at 5 cm above the anal verge, the recording tip will usually be in the rectal ampulla, and at 4 cm , it will be in the ampulla about half the time Thus the hump of the pressure profile may not be as significant as it appears to be Following anesthesia, furthermore, pressures at the upper recording sites (4 and 5 cm) decreased, a finding which was "taken to indicate a general muscular relaxation affecting intra-abdominal pressure rather than any specific local effect on the ano-rectal musculature " Harris and Pope would argue that the decreased pressure found intra-anally after anesthesia merely reflected the decreased intraluminal pressure to which the recording tips were exposed before they were drawn into the anal sphincter zone

One's immediate reaction, of course, is to ascribe the different results obtained to differences in instrumentation, but Harris maintains he has used open and balloon-covered tips as well as recording tubes of various rigidity without significantly affecting his results At present, it would be rash to say which view is correct, possibly time will show that there is some truth on both sides. The entire intraluminal pressure recording fraternity is challenged, however, by the findings and interpretations presented in the following article, and it will become necessary to confirm or deny the views there expressed —Ed]

"Squeeze" vs. Resistance: Evaluation of Mechanism of Sphincter Competence. Many articles dealing with intraluminal pressure at the gastroesophageal junction imply that the high-pressure zone recorded within this junctional region acts as a pressure barrier separating the adjacent cavities, and that the height of the pressure within the junctional region may be correlated with gastroesophageal sphincter competence. It seemed unlikely to Lauran D. Harris and Charles E. Pope II[2] (Boston Univ.), however, that a pressure could separate two cavities or, indeed, that any pressure should exist in the potential lumen of a closed sphincter. To elucidate the mechanisms responsible for such intrasphincteric pressures as are measurable, they chose the anal sphincter as readily accessible to repeated study. Two open-tipped, side-opening polyvinyl catheters with recording orifices 5 cm. apart were used under various conditions to study

(2) J Clin Invest 43 2272 2278 December 1964

intra-anal and intrarectal pressures in normal subjects lying on their left sides.

When the recording tips were placed in the rectal ampulla and were then withdrawn through the anal sphincter to the outside, they recorded, successively, pressures of 5-10 mm. Hg that were subject to respiratory variations, a pressure plateau 2-6 mm. Hg higher than mean ampullary pressure but not showing respiratory variations, and atmospheric pressure. The pressure plateau extended 3-5 cm. and was regarded as the zone of the anal sphincter. When the entire withdrawal procedure was repeated while the subject performed a Valsalva maneuver, pressure in the ampulla rose, and pressure in the sphincter zone was commensurately higher, thus apparently maintaining a sphincter-ampulla pressure gradient. However, if the subject terminated the Valsalva procedure, when the upper recording tip was still in the rectal ampulla and the lower tip in the sphincter, the upper tip showed a prompt drop in pressure, but the intrasphincteric tip continued to record an unchanged high pressure. Further, if a recording tip was placed in the anal sphincter zone before the Valsalva maneuver was initiated, no pressure rise was recorded when the subject began this procedure, though ampullary pressures rose sharply.

Further studies showed that somewhat lower intrasphincteric pressure plateaus were measured when the recording tip was pushed from the outside into the anal sphincter than if it was withdrawn into the sphincter from the ampulla. If ampullary pressure was made negative by having the subjects standing on their heads, sphincteric pressure recorded when the tip was pulled from such a zone of negative ampullary pressure into the sphincter was similarly negative with respect to atmospheric pressure.

A variety of tests was carried out to determine whether or not the results might be related to an artifact of assembly structure, but the results were qualitatively the same whether the recording tips were side opening, end opening or covered by a small balloon. The tubing used to transmit pressures was also varied by using stiffer polyethylene tubing and even stainless steel tubing, but the findings remained the same. Thus, it did not appear that the compliance of the recording system or other features of its construction were responsible for the results.

The results were not consistent with the idea that intrasphincteric pressure provided a barrier between ampulla and outside, since this pressure varied widely depending on what maneuvers were used to elicit it, and especially since under certain conditions an apparently negative intrasphincteric pressure could be recorded. The only reasonable explanation for the results is that intrasphincteric pressures have no physiologic meaning but are merely a function of the last pressure to which the recording tip is exposed before entering the sphincteric zone. The squeeze of the sphincter thus merely acts to seal off the recording system.

THE LIVER

Origin and Fate of Proliferated Hepatic Ductal Cells in the Rat: Electron Microscopic and Autoradiographic Studies were carried out by J. W. Grisham and E. A. Porta[3] (Washington Univ.) to resolve the longstanding controversy as to whether or not biliary epithelial cells and hepatocytes are able to transform, one into the other. Rats were subjected to various procedures known to cause proliferation of ductal cells and/or hepatocytes, e.g., dietary deficiencies, ethionine, α-naphthylisothiocyanate, hepatectomies of various types and extrahepatic biliary tract obstruction. Rats so treated were killed after various time intervals, and liver tissues were studied by electron microscopy and by autoradiography after injection of tritiated thymidine.

Normal ductal cells and hepatocytes differ distinctively when examined by electron microscopy. As compared with hepatocytes, ductal cells are usually more than one-half smaller, the nuclear material shows a different distribution, mitochondria are smaller and fewer in number, endoplasmic reticulum and glycogen are scanter, and centrioles may be noted in close relationship to ductal cell nuclei. In addition, ductal cells tend to form tubules and show no unusual relation to blood capillaries. At points of connection of the smallest ducts with canaliculi, the sharp and abrupt change

(3) Exper & Molecular Path 3 242 261, June, 1964

in cell type may be well seen. Proliferating ductal cells, stimulated by the methods outlined, retain their distinctive characteristics, and although the responses to injury produce some alterations in both ductal and parenchymal cells, these changes are never of such degree as to produce transition forms which cannot be classified as either cell type. Both ductal cells and hepatocytes, however, have microvilli projecting into the lumens of ducts and canaliculi, respectively.

When tritiated thymidine was injected into rats at times when ductal or polygonal cell proliferation had been stimulated, the label appeared abundantly in the cell type which was proliferating. Maximal proliferation of hepatocytes and of ductal cells, moreover, was often asynchronous, and there was no evidence with passage of time that the label was transferred from one cell type to another. Once the agent producing increased ductal cell proliferation was removed, these cells became fewer. Since the label did not appear in either newly dividing ductal cells or in hepatocytes, ductal cells apparently died and were removed.

Neither electron microscopy nor autoradiography indicates that transformation of hepatocytes to ductal cells, or vice versa, occurs.

[By somewhat similar radiographic technics, E. Rubin (Exper. & Molecular Path. 3:279, 1964) also found that ductules produced by chronic hepatic injury do not derive from hepatocytes or mesenchymal cells. However, he found no evidence that they came from bile duct epithelial cells and thus concluded that proliferating ductules probably originate from pre-existing cells of the canal of Hering. Grisham and Porta suggest that all cells lining the intrahepatic biliary channels, whether those of major ducts or of ductules, may be considered a homogeneous class. – Ed.]

Infectious Hepatitis—A Generalized Disease: Study of Renal, Gastrointestinal and Hematologic Abnormalities is reported by Marcel E. Conrad, Franklin D. Schwartz and Allen A. Young[4] (Walter Reed Army Inst. of Res.). Subjects were 25 United States servicemen with viral hepatitis who were admitted consecutively to a hospital in Korea. Each had been jaundiced for less than 5 days before admission, and the diagnosis was established by the clinical course, the elevated bilirubin and serum transaminase levels and liver punch biopsy. Within 1 month after onset of illness, each patient was evacuated to the Walter Reed General Hospital and there hospitalized until judged recovered. Sixteen subjects were re-examined 1 year after onset of illness. Three

(4) Am. J. Med. 37:769-801, November, 1964.

biopsy specimens of the intestine and the liver were obtained during the first 100 days of illness, and repeat biopsies were performed on subjects returning 1 year later.

The course of the patients' illness and the pattern of laboratory and hepatic structural abnormalities was typical of the range of findings characteristically seen in viral hepatitis. Seven had laboratory evidence of relapse, and in 2 of the 7, liver biopsy showed evidence of recurrent hepatitis. At the 1-year biopsy, normal liver structure was found in all but 3 subjects One had fatty metamorphosis; 1, mild residual scarring of the portal triads; and 1, periportal mononuclear infiltrates.

Hematologic studies showed that anemia (hematocrit less than 40%) developed in 19 patients during the 2d and 3d week of hospitalization, with a subsequent return to normal values. Reticulocyte counts increased during the 1st to 2d weeks and reached maximal elevations during the 3d to 4th weeks. In 6 patients, reticulocytosis persisted for more than 2 months, and in 5 of these, there was a decreased red cell survival, with a red cell half-life of 16-20 days. Coombs tests were negative. At the 1-year follow-up, reticulocytosis and indirect hyperbilirubinemia were found in only 1 patient Four had elevated leukocyte counts (12,000-18,000/cu mm.) during the 2d week of illness.

Urinalysis showed abnormal amounts of protein in random urine specimens from 15 patients. Hematuria of more than 5 red cells per high-power field was seen in 10, and 2 of these had red cell casts. Pyuria (5-10 white blood cells per high-power field) was present in 12. The urinary abnormalities disappeared after the 10th hospital day.

Intestinal biopsies showed lymphoid infiltration of the villous stroma and lamina propria with lymphocytes, histiocytes and plasma cells. During the early stages, irregular and club-shaped villi appeared among normal processes. With prolonged illness, the mucosal cells became flattened and the cytoplasm of the covering epithelium frequently appeared fused (Fig. 68). Goblet cells increased in number. The crypts appeared prominent and contained many Paneth's cells Many large, broad villi were seen, apparently representing fusion of several villous processes. Three of 8 gastric biopsy specimens showed lymphocytic infiltration and edema of the submucosa.

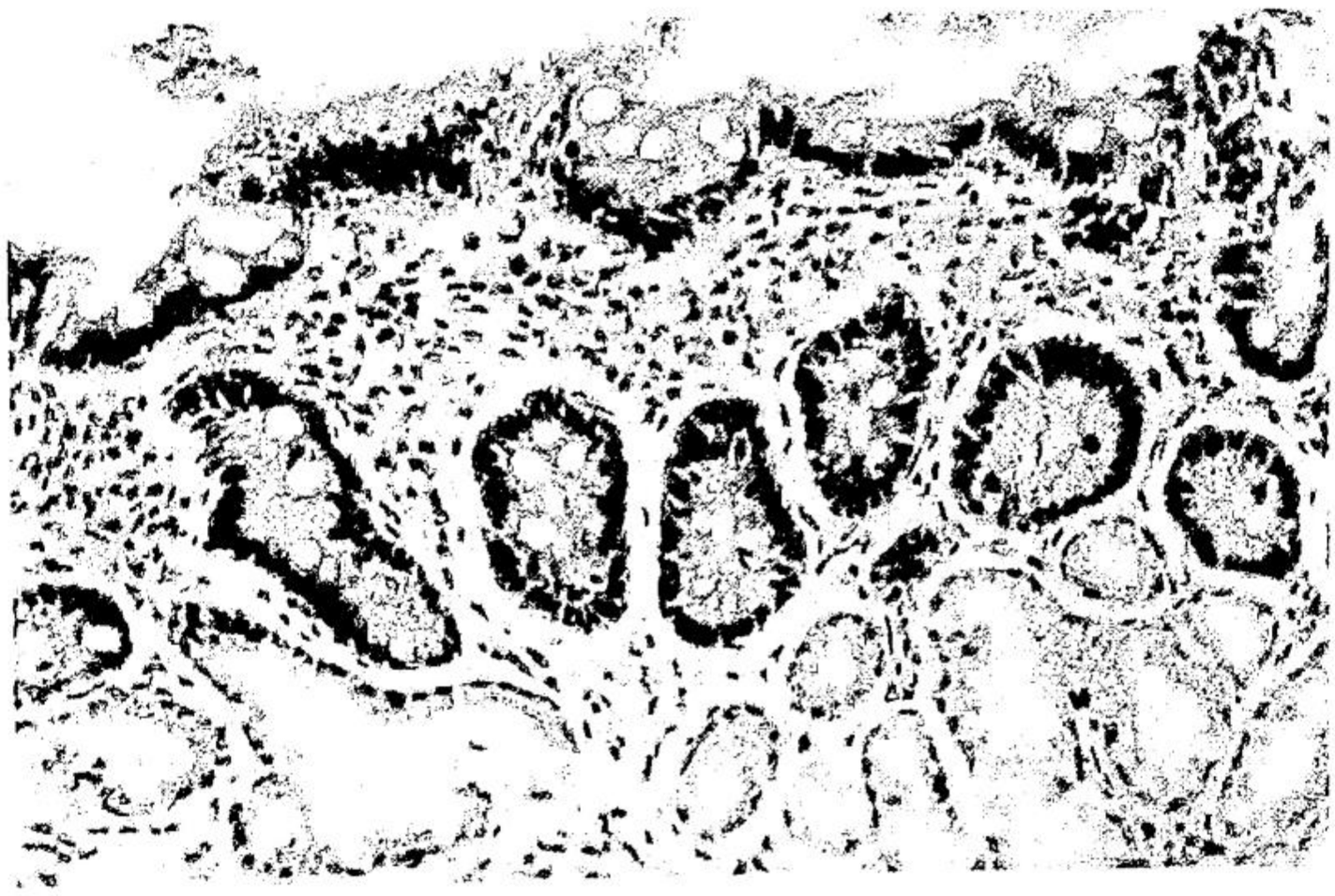


Fig. 68 - Progression to patchy flattening of the mucosal surface of the gut (Courtesy of Conrad M E. *et al.* Am J Med 37 789 801, November 1964.)

Percutaneous renal biopsies, performed on 20 patients during the acute stage of illness, showed no pathognomonic lesions, but all showed histologic alterations. Most common were hyaline granular tubular changes, diffuse interstitial edema and deposition of protein in Bowman's spaces. Mild glomerular lesions were seen in 10 specimens and consisted of diffuse glomerular swelling in focal areas of hypercellularity. At the 1-year follow-up, kidney biopsy specimens from 5 patients showed no abnormalities.

The changes observed involving multiple organs were believed to be the result of viral hepatitis, as other causes of jaundice producing illness, such as leptospirosis and infectious mononucleosis, were excluded by appropriate tests. The results indicate that infectious hepatitis should be considered a generalized disease with almost invariable involvement of the gut, frequent involvement of the renal and hematologic systems, and, in all probability, involvement of other organs that were not studied.

► [The finding of villous atrophy with alterations in the epithelium and stromal infiltration during the acute phase of infectious hepatitis is confirmed by a study reported by Astaldi *et al.* (Am. J. Digest. Dis. 9 237, 1964), and according to Sheehy *et al.*, the changes may be severe enough to cause steatorrhea (J.A.M.A. 190:1023, 1964). It would seem, however, that in a patient with acute hepatitis, an inadequate supply of bile salts cannot be ignored as a possible explanation for any steatorrhea that is detected.—Ed.]

Viral Hepatitis in a Group of Boston Hospitals: II. Prospective Controlled Epidemiologic Study. A retrospective review of the records of 1,675 patients with hepatitis hospitalized in Boston from 1951 through 1962 had revealed that

TABLE 1 - SIGNIFICANCE OF POTENTIAL EXPOSURES TO HEPATITIS WITHIN 15-60 DAYS OF ONSET

POTENTIAL EXPOSURE	NO. AMONG 75 PATIENTS EXPOSED	NO. AMONG 75 CONTROLS EXPOSED
Jaundiced persons	15	0*
Children, 2-14 yr old	54	47
Sick children	33	20
Cockroaches	12	12
Out of state travel	26	15
Restaurant food	63	64
Raw-shellfish ingestion	16	4*

*P < 0.02

two-thirds had acquired the disease without evidence of exposure to conventionally recognized sources, such as transfusions or jaundiced persons. Since retrospective studies may provide an incomplete picture, a prospective study was begun in 1963 at 10 Boston hospitals by George F. Grady, Thomas C. Chalmers and the Boston Inter-Hospital Liver Group[5] to determine whether potential exposures to icterogenic agents or situations occurred more often among 100 patients with hepatitis than among 100 matched controls. An attempt was made to include all patients over age 15 years whose working diagnosis was acute infectious or serum hepatitis. It was estimated that 50% of Boston patients hospitalized with hepatitis during the period of study were included.

Each patient was interviewed to determine whether potential exposures to viral hepatitis had occurred by oral means within 15-60 days or by parenteral routes within 15-180 days. Control patients were selected from those admitted for acute surgical problems such as fractures and appendicitis. They were pair-matched with the hepatitis patients on the basis of sex, race, age, marital status, hospital accommodation and hospital-admission dates.

Of the patients with hepatitis, 25 had been recently transfused, 15 had been exposed to jaundiced persons, and in the other 60, the source of hepatitis was less apparent. The mean age of the 25 patients suspected of having posttransfusion hepatitis was about 50. About a third of these patients had a

(5) New England J. Med. 272 662-666. April, 1965

concurrent or prior nonhepatic illness, and 12% had a fatal outcome.

Analysis of possible sources of exposure in the remaining 75 patients and their controls showed that a significant difference existed only with respect to exposure to jaundiced persons and ingestion of raw shellfish, usually clams (Table 1). Exposure of these 75 patients and their controls to tissue penetrations was about the same. The sum of injections by physicians was significantly greater in the patient than in the control group, but this difference was chiefly based on the fact that 2 patients had received a total of 27 injections (Table 2).

Analysis of symptoms indicated that the 25 patients who had had transfusions and the 3 who had had a clear history of inoculations usually noticed an insidious onset with minimal prodromal symptoms or fever. In contrast, 18 patients who were thought to have infectious hepatitis on convincing epidemiologic grounds frequently had clear-cut onset of prodromal symptoms consisting of fever, nausea, gastrointestinal disorders, cough, coryza, pharyngitis, lymphadenitis, myalgia and photophobia.

Although epidemiologic studies such as this are subject to many errors, the causal role in transmission of viral hepatitis of ingestion of contaminated raw shellfish and of tissue

TABLE 2.—SIGNIFICANCE OF TISSUE PENETRATIONS WITHIN 15-180 DAYS BEFORE ONSET OF HEPATITIS

POTENTIAL EXPOSURE	CASES AMONG 75 PATIENTS	CASES AMONG 75 CONTROLS
Visit to dentist	20	25
One or more injections by dentist	7	11
Sum of injections by dentist	12	19
Visit to physician	28	29
One or more injections by physician	11	8
Sum of injections by physician	47	13*
Total persons receiving injection	27	20
Sum of injections received from physicians, dentists and any other source*	95	51*

*Excluding 2 diabetics addicts and their controls.
*$P < 0.01$.

penetrations with contaminated equipment appears to be confirmed. On the other hand, dental procaine injections and cockroaches could not be incriminated Also, it has been again shown that onset of orally transmitted infectious hepatitis and parenterally transmitted serum hepatitis present different clinical features.

Posttransfusion Anicteric Hepatitis. Reported attack rates of hepatitis after transfusion vary greatly and range from 6 to 200 cases per 10,000 units of blood transfused. To study this problem further, Constantine L. Hampers, David Prager and John R. Senior[6] (Philadelphia Gen'l Hosp) selected 56 women who had received 1 or more units of blood on a single day and who had, on the basis of history and tests, no evidence of pre-existing hepatic disease. Serum activities of glutamic oxalacetic and glutamic pyruvic transaminases and isocitric dehydrogenase were assayed immediately before or shortly after the transfusions. The patients were re-examined and blood samples were drawn 3 or 4 weeks after transfusion, then every 2 weeks for 12 weeks and finally every month until at least 6 months had elapsed. Twenty-five patients who received no blood products were chosen randomly from the same patient population and were followed concurrently with the transfused patients.

A patient was suspected of having hepatitis if elevations greater than 3 S.D. above the normal mean of all three of the enzyme activities determined were found on repeated assays. On this basis, evidence of hepatitis developed in 10 (18%) of the 56 patients but in no control. In 2 patients serum enzyme elevations developed in less than 5 weeks, but in the rest increased levels were found 60-100 days after transfusion. Whether or not those with the short incubation period represented cases of serum hepatitis or parenterally transmitted infectious hepatitis could not be established. Enzyme levels returned to normal in 3-19 weeks in 8 patients. In 2, however, elevations recurred for 10 and 11 months.

None of the patients was icteric clinically or chemically, and the only consistently positive liver function test was an increase in bromsulfalein retention in all 6 of the patients in whom it was measured. Six patients had clinical symptoms Six patients (including 4 with symptoms) were hospitalized.

(6) New England J Med 271 747 754 Oct 8 1964

in these liver biopsy showed minimal to moderate changes consisting of periportal and intralobular inflammatory infiltration. Moderate liver cell degeneration was seen in 2 biopsies. There was a rough correlation between the degree of these histologic changes and the degree of serum enzyme elevations The 2 patients with persisting enzyme abnormalities also had persisting histologic abnormalities on repeat liver biopsy.

A review of icteric cases of serum hepatitis diagnosed in the Philadelphia General Hospital during 4 years showed an incidence of only 5 cases per 10,000 transfusions. The present study thus suggests that there may be over 100 cases of anicteric hepatitis in this hospital for each icteric case diagnosed. The high incidence of anicteric hepatitis found could not be blamed on the type of blood donor used; of the 44 donors whose blood was given the 10 patients who acquired hepatitis, less than 20% were professional donors.

► [Grady and Chalmers in a survey of the incidence of hepatitis in Boston hospitals over a 10-year period (New England J Med 271 337, 1964) found only 1 case of hepatitis for every 1,775 units of blood transfused The mortality, however, was high- 12% The obvious explanation for the difference between this low attack rate and the high one reported by Senior and his associates is obvious Grady and Chalmers are writing about clinically recognized hepatitis, whereas Senior is writing about what might be called "transaminase hepatitis."

But is anicteric "transaminase" hepatitis the same disease as the hepatitis which we recognize clinically? On the face of it, one would be inclined to state it was, but there really is no evidence Thus a group working in Hans Popper's laboratory, in discussing a common form of anicteric "transaminase" hepatitis in Korea, are duly cautious and take great pains to point out that the viral etiology of the cases they describe "is far from established" (Gastroenterology 48 1, 1965) – Ed.]

Benign Postoperative Intrahepatic Cholestasis is described by Martin Schmid, Max L. Hefti, Ruth Gattiker, Hans J. Kistler, and Åke Senning[7] (Univ. of Zurich) on the basis of the clinical course of 12 patients who developed a postoperative bilirubin level of 5 mg./100 ml. or over. The typical course of such postoperative jaundice is presented by the following case.

Man, 58, had removal of most of the upper stomach with an esophago-antral anastomosis and incidental splenectomy because of carcinoma of the cardia. During the operation, 1,800 ml. blood was given. Jaundice without pruritus or hepatosplenomegaly appeared on the 1st hospital day. The urine contained bile pigment and traces of urobilinogen. Maximum bilirubinemia of 10.8 mg./100 ml., with

(7) New England J. Med. 272: 549-559, Mar. 18, 1965.

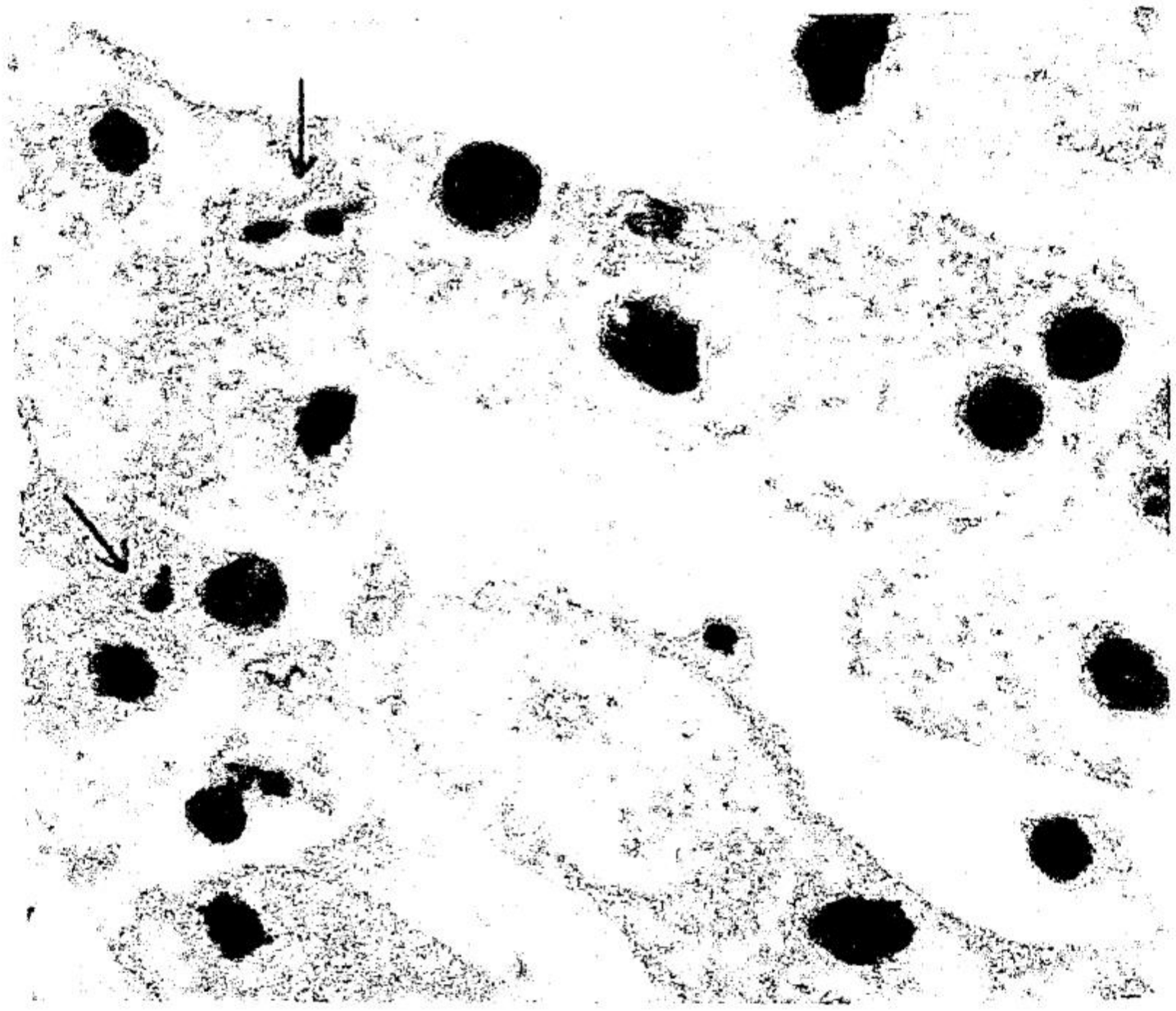


Fig 69 —Needle biopsy of liver showing centrilobular bile stasis and slight vacuolar changes in the cytoplasm of many liver cells Arrows point to bile casts in dilated canaliculi (Courtesy of Schmid M *et al* New England J Med 272 543 550 Mar 18 1965)

5 1 mg 100 ml in the conjugated form, occurred on the 6th postoperative day Various tests of hepatic function yielded normal or near normal results, but the alkaline phosphatase was 18 5 Bodansky units Three weeks later, the serum bilirubin returned to normal

A similar picture was seen in all 12 cases. Jaundice usually appeared on the 1st or 2d postoperative day, but in 2 cases appeared on the 5th and 11th days, respectively. It usually reached maximum intensity on the 3d to 7th day and disappeared within 3 weeks after the operation Fever was not part of the picture, and the liver and spleen were not enlarged Except for 1 patient who had symptoms suggesting a penicillin reaction, no allergic manifestations were seen.

Laboratory studies also showed a consistent pattern Maximum serum bilirubin values ranged from 5.4 to 27 6 mg 100 ml., with about two-thirds being the conjugated fraction. Bile pigment was present in the urine, but urobilinogenuria was variable Transaminase values were either normal or slightly elevated on the 1st day after operation, the highest SGO-T value recorded being 165 units. The alkaline phosphatase exceeded 10 Bodansky units in 5 cases. In all cases, serum protein levels and flocculation tests were normal. No blood coagulation defects were seen, the blood picture was non-

specific, and there was no proof of acute intravascular hemolysis.

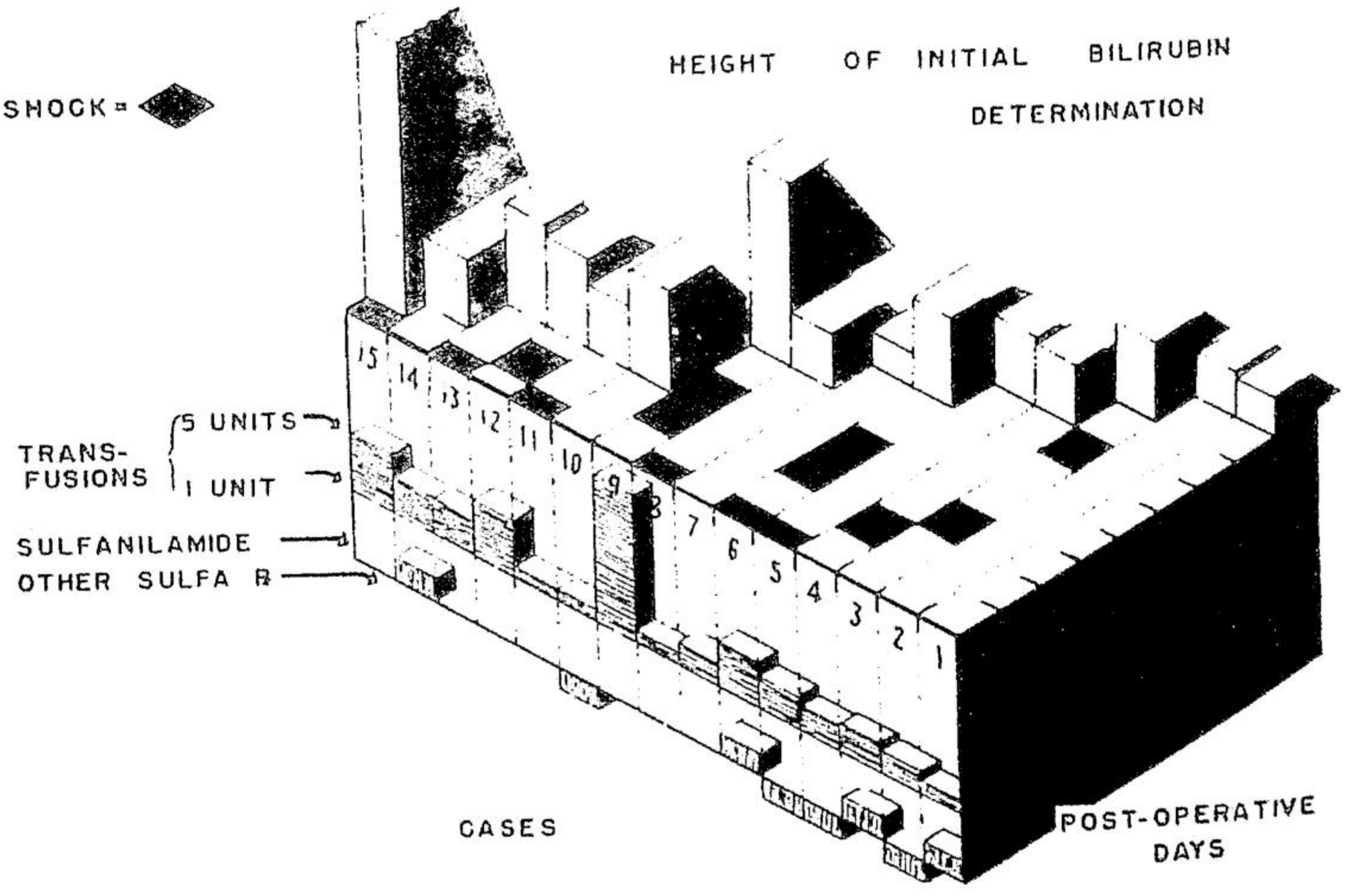
Liver biopsy in 9 patients and autopsy in 2 uniformly revealed the typical signs of cholestasis: dilated canaliculi in the centers of lobules containing bile casts (Fig. 69). Slight vacuolar changes were seen in the cytoplasm of the liver cells, and biliary pigment was found within both liver and Kupffer cells. Signs of liver cell damage were slight and inflammation was absent.

Without exception, the operations preceding the jaundice were long and difficult. More than half the patients were regarded as poor risks, but only 1 had evidence of pre-existing hepatic disease. Ten patients had halothane anesthesia. Only 2 patients had short episodes of hypotension during the operation All 12 patients received blood transfusions, the mean age of transfused blood being 10 days. With the exception of 1 patient, antibiotics and sulfonamides were not administered before or after the operation until onset of jaundice

Although many patients had halothane anesthesia, the hepatic pathology in these patients differed radically from that ascribed to halothane toxicity. In addition, posthalothane jaundice produces a severe clinical picture not seen in the patients described in this series Finally, 2 of the patients had not received halothane

There was no evidence that the reaction was related to antibiotics or sulfonamides, to transfusions or other injections or to intravascular hemolysis. On the other hand, blood from transfusions that is more than 3 weeks' old breaks down rapidly in the first 24 hours after transfusions, and others have ascribed jaundice to administration of old bank blood In the 12 cases studied, however, there was no correlation between amount of blood transfused and the height of the bilirubin level subsequently attained Thus the syndrome is believed to be the result of transient hepatic secretory insufficiency resulting from the surgical procedure, but the exact responsible mechanism remains unknown.

► (About 1943-49 we saw 15 cases of postoperative jaundice similar to the cases here described, and we also were impressed that a type of postoperative jaundice, not attributable to any known mechanism, occurred under various circumstances. As the number of transfusions and the high incidence of operative or postoperative shock (accompanying illustration) suggests, the



operations were all serious Bilirubinemia was noted from 1 to 8 days postoperatively Although medications of various types, particularly sulfonamides, were given the reason for citing our cases is the fact that halothane was *not* given to any of them, thus supporting the contention of Schmid *et al* that their cases were not the result of halothane toxicity

We did not publish our studies because of two major defects We had neither hepatic biopsy specimens nor studies of red blood cell breakdown Schmid and his co workers have corrected one of these defects in examining hepatic tissue histologically Unfortunately, they also have no data on the rate of hemolysis, and their remarks concerning old bank blood must remain speculative It seems quite definite, however, that there is a type of benign postoperative jaundice which is probably the result of an impairment of hepatic excretory function but is brought to light by an excess load of bilirubin pigment released by the rapid breakdown of old bank blood – Ed.]

Jaundice during Treatment with Oral Contraceptive Lyndiol is reported by Goran Cullberg, Rolf Lundstrom and Unne Stenram.[8]

Woman, 39, was a para -2 who had had pyelitis during her first pregnancy She began taking 1 tablet of Lyndiol (0 15 mg mestranol and 5 mg lynestrenol) daily in July, 1964 Three or 4 days later she had nausea and vomited, but she took the tablets for 10 more days She gradually lost her appetite, became tired and began to itch At the end of July the urine became dark, and she was hospitalized Jaundice reached its maximum after the middle of August (total bilirubin 8 4 mg 100 ml with 7 52 mg direct acting) and then gradually subsided She left the hospital on September 18, and follow-up on October 7 showed her to be well Maximum serum

(8) Brit M J 1 695-697 Mar 13, 1965

alkaline phosphatase was 76 units (normal 2-8). Thymol turbidity was 8.5 units, serum pyruvic glutamic transaminase was 230 units and serum glutamic oxalacetic transaminase was 52 units. Electrophoresis of serum proteins yielded essentially normal results. The hemoglobin level was 9.33 Gm./100 ml., and the white blood cell count was normal. Osmotic fragility of erythrocytes and a Coombs test were normal.

Biopsy on September 8, when jaundice was subsiding, showed slight distortion of liver cells with variation in size and a few balloon forms. Nuclear patterns were also slightly deranged, with several multinucleated cells being seen. Inflammatory cells in the portal tracts were minimal. There were many bile thrombi in the biliary canaliculi, and bile pigment was present in parenchymal and Kupffer cells. No fatty change was evident.

The patient was believed to have jaundice caused by the oral contraceptive agent because (1) she had received no injections for over a year, (2) she had had no contacts with other cases of jaundice and (3) other cases have been reported as being caused by oral contraceptives. These agents have contained 3-methoxy ethinyl estradiol, norethindrone, norethynodrel, norethisterone acetate, ethinyl estradiol, mestranol, lynestrenol and megestrol. The jaundice that has followed use of these agents has been characterized by cholestatic phenomena such as itching and elevated serum alkaline phosphatase levels, further, as in the case reported, there has been some cytotoxic effect as evidenced by elevated serum transaminase levels and cellular changes on histologic examination.

► [As Sherlock points out in a review entitled "Jaundice Due to Drugs" (Proc. Roy. Soc. Med. 57:881, 1964), C-17 alpha-substituted testosterone derivatives such as methyl estranolone, methandienone, norethandrolone, norethisterone and norethynodrel are recognized as causing jaundice resembling that caused by methyl testosterone, and C-17-alpha-substituted agents are commonly used as components of antiovulatory preparations. It is apparent, however, that the jaundice which is attributed to such agents is not purely cholestatic in that liver biopsy may show some cellular changes and liver function tests, transient elevations of transaminase levels.

In addition to synthetic 17 alpha substituted compounds, it has been shown recently that natural estrogens such as estradiol and estriol may depress the hepatic secretory transport of bromsulphalein (J. Clin. Invest. 43:1905, 1964), an action resembling that attributed to the 17 alpha-substituted steroids. Perhaps, under certain conditions such as enhanced individual susceptibility (as the patient with recurrent jaundice of pregnancy may have), synthetic and natural steroids may combine to cause hepatic damage which goes beyond the mere impairment of hepatic excretory function. – Ed.]

Cholestatic Jaundice Complicating Pregnancy: Recurrence after Norethynodrel with Ethinyl Estradiol (Enovid). Cholestatic jaundice associated with marked pruritus has been noted during the last trimester of pregnancy. The jaundice is obstructive, and all manifestations of the disorder disappear after delivery. A. J. Elliott and J. Hendry[9] (Bran-

[9] Canad. M. A. J. 92:344-345, Feb. 13, 1965.

don, Man., Gen'l Hosp.) observed a patient so affected and found her course particularly noteworthy in that she had a recurrence of jaundice when she was not pregnant but was taking Enovid.

Woman, 26, had had marked pruritus during each of her 3 pregnancies, particularly in the last trimester Jaundice was not noted during her first 2 pregnancies, but during the third she had a total serum bilirubin of 3 8 mg /100 ml , with a direct-reacting fraction of 2 6 mg./100 ml Alkaline phosphatase was 19 King-Armstrong units, and the serum glutamic oxalacetic transaminase (SGO-T) was 104 units. Liver biopsy 9 days after delivery showed a completely normal architecture with no evidence of bile stasis Within a few weeks, the patient felt completely well, and a cholecystogram, taken after recovery, was normal About 14 months later the patient began taking Enovid, 1 tablet daily After 14 days she experienced some nausea and vomiting and noted that her urine was dark. Within 3 days she became clearly jaundiced and had marked pruritus After Enovid was discontinued, pruritus lessened but jaundice persisted Three weeks after onset of jaundice total serum bilirubin was 6.3 mg /100 ml , with a direct-reacting fraction of 4 mg /100 ml., alkaline phosphatase was 13.7 King-Armstrong units and SGO-T was 50 units. Oral prednisone was given for 2 weeks, and by 1 month after onset of jaundice the patient was feeling well without itching and had no dark urine.

The episodes of jaundice in this patient were probably hormone induced and involved hormones produced naturally during pregnancy and those given as medication. The occurrence of jaundice in the latter part of pregnancy would correspond to the time when the levels of estrogen and progesterone-like substances are highest. A similar picture developed on a second occasion when the patient was given a preparation containing a combination of these two hormones.

Oral contraceptives have been incriminated by others as occasionally causing jaundice. On the other hand, the large number of women who have taken antiovulatory agents without apparent ill effect tends to discount such agents as important causes of jaundice.

Prolonged Neonatal Unconjugated Hyperbilirubinemia Associated with Breast Feeding and a Steroid, Pregnane-3α, 20β-Diol, in Maternal Milk That Inhibits Glucuronide Formation In Vitro was studied in 7 full-term, unrelated, newborns by Irwin M. Arias, Lawrence M. Gartner, Sam Seifter and Mathilda Furman[1] (Albert Einstein College of Medicine). Known causes of prolonged neonatal jaundice were excluded

(1) J Clin Invest 43 2037 2047, November, 1964

by appropriate tests. The mothers and the course of the pregnancies were considered to be entirely normal. Mild jaundice was noted in 4 infants during the first 4 days but was diagnosed as physiologic hyperbilirubinemia. Mothers and babies were discharged from the hospital between the 4th and the 7th days. However, progressively increasing jaundice was observed thereafter by each mother in her infant, and 5 babies were rehospitalized on days 9-14. Examination of the babies revealed intense jaundice but no hepatomegaly, splenomegaly, fever, pallor or neurologic changes. Maximal serum unconjugated bilirubin concentrations ranged from 14.3 to 24.5 mg./100 ml. and were observed on the 10th to the 19th days. In no case did the direct-reacting bilirubin exceed 10% of the total.

In 4 infants, breast feeding was abruptly terminated, and the serum bilirubin concentration became normal in 3-6 days. One mother continued breast feeding; during this time the infant's serum bilirubin dropped from 17 mg./100 ml. on the 11th day to a normal value on the 35th. Another mother fed her baby from the 2d to the 9th days, at which time the infant's serum bilirubin was 16 mg./100 ml. Breast feeding was discontinued for 4 days and evaporated milk substituted. During this time the infant's serum bilirubin decreased to 5.5 mg./100 ml. When breast feeding was reinstituted, the infant's serum bilirubin concentration remained at 5-5.8 mg./100 ml. for 5 days and was 2.5 mg./100 ml. on the 20th day.

The 7 mothers of these infants had had 13 previous children, 7 of whom had been breast fed. Prolonged jaundice had been observed in 6 of these 7, but no jaundice had been seen in the 6 bottle-fed infants. These observations suggested a strong relation between breast feeding and severe, prolonged neonatal unconjugated hyperbilirubinemia.

The glucuronyl transferase activity of guinea pig liver homogenates, using o-aminophenol as a glucuronide receptor, was tested in the presence of milk from the mothers of the jaundiced children and of milk from control mothers. The milk of the patients' mothers inhibited transferase activity by 79 ± 6.5% (1 S.D.), as opposed to an inhibition of 11 ± 4.1% by the milk from the controls. The formation of direct-reacting bilirubin by slices or homogenates of human, guinea pig and rat liver was also inhibited 41% or more by

the milk of mothers from the jaundiced infants, as opposed to a control figure of 9.4% or less. No evidence could be obtained that serum from the mothers of the jaundiced infants, or serum from control mothers, or milk obtained from pregnant and postpartum Jersey, Guernsey and Holstein cows affected the glucuronidation rate by guinea pig liver homogenates of o-aminophenol

By a variety of extraction procedures, a crystalline material was obtained from the milk of 3 mothers of jaundiced infants. The infrared spectrum of the isolated crystalline material was identical with that of pregnane-3α, 20β-diol and significantly different from that of pregnane-3α, 20α-diol The glucuronide-conjugating ability of guinea pig homogenates with respect to o-aminophenol was equally inhibited by addition of pregnane-3α, 20β-diol and pregnane-3α, 20α-diol.

These studies show that some mothers secrete in their milk a steroid that inhibits glucuronyl transferase activity in vitro. The source of this steroid, identified as pregnane-3α, 20β-diol, is not known. It does not appear in excess in the serum of the mothers involved, and thus the jaundice in the infants is quite different from the nonhemolytic unconjugated hyperbilirubinemia affecting infants in the first 4 days and characterized by the presence in the mothers' serum of a high level of unidentified substances that inhibit glucuronyl transferase activity.

Pregnane-3α, 20β-diol probably competes with bilirubin for transferase activity and thus produces jaundice. This jaundice tends to subside, even if breast feeding is continued. Whether this is to be ascribed to decreased amounts of inhibitory substance in the milk or increased glucuronyl transferase activity in the infants' liver is not known, but inhibitory activity in the mother's milk may be found as long as 4 weeks post partum.

Comparative Study of Four Methods of Determining Alkaline Phosphatase. Julius J. Deren, Louis A. Williams, Hugo Muench, Thomas Chalmers and Norman Zamcheck,[2] with the technical assistance of Priscilla Stevens, compared the technical reliability of the Bodansky, King-Armstrong, Bessey-Lowry and Klein methods and described the relation

(2) New England J Med 270 1277 1283 June 11, 1964

Conversion Factors

Conversion from	Conversion to Bessey-Lowry	Conversion to Bodansky	Conversion to King Armstrong
		multiply by	
Bessey Lowry		1 3 (multiply & divide by 1 8*)	3 5 (multiply & divide 2 0)
Bodansky	0 79 (multiply & divide by 1 6)		2 8 (multiply & divide 1 9)
King-Armstrong	0 29 (multiply & divide by 2 0)	0 34 (multiply & divide by 1 9)	

*Multiplication and division factors represent 95% confidence limits of conversion factor

among the four tests over the clinical range of serum phosphatase activity.

A total of 215 blood samples were drawn from patients at various Boston hospitals. The samples were centrifuged, and aliquots of serum were placed in two tubes, identified by random numbers and kept frozen until analyzed. Freezing for 2 months did not affect the values obtained.

Laboratory variability was tested by two methods. In the first, 2 samples of serum, 1 at a high and the other at a low level of alkaline phosphatase activity, were selected, and 10 determinations were done by each of the four methods on a single day by one laboratory technician. The coefficient of variation ranged from 3.3 to 7.4%, and results were not significantly different for the four methods tested.

The second test consisted of duplicate determinations performed on 48 samples of serum by each method in a double-blind fashion on different days by the same laboratory technician. This evaluation should provide an estimate of variability of alkaline phosphatase values as they may be reported to the clinician on the wards. The 95% confidence limits for the Bessey-Lowry, Bodansky and King-Armstrong methods ranged from 50% greater to 33% lower than the value reported. The Klein variability was greater, especially at low values.

Reasonably linear relations were obtained when the Bessey-Lowry, Bodansky and King-Armstrong methods were plotted against each other, and the conversion factors so obtained are shown in the table. The Klein method did not bear a straight-line relation to the other three methods. Use of such conversion factors, however, increases the range of the 95% confidence limits.

When the results of the four methods were plotted against the disease states of the patients from whom the samples were taken, the four methods appeared equally reliable for detection of disease and, with the exception of the Klein method, manifested a proportional deviation from normal values. Thus, the results of the study do not warrant a preferential choice among the Bodansky, King-Armstrong and Bessey-Lowry methods.

► [Doctors and editors of medical journals are funny people Here is an article certainly designed to serve a most practical purpose and published in one of the most popular medical journals of today Yet, despite this orientation, the article is so full of statistical jargon that the untrained reader has difficulty in understanding what was done —Ed.]

Comparison of Serum Aminopeptidase and Alkaline Phosphatase in Detection of Hepatobiliary Disease in Anicteric Patients was made by Alexander M. Rutenburg, Benjamin M. Banks, Esteban P. Pineda and Julius A. Goldbarg[3] (Boston) on the basis of serum enzyme values found in 400 anicteric patients in whom the diagnosis of hepatic, biliary or pancreatic disease was established by standard clinical and laboratory criteria or by histologic examination. Of 158 patients who had hepatic metastases from various organs, 82% had elevated serum leucine aminopeptidase (LAP) and 63% elevated alkaline phosphatase. Only 1 patient had an elevated alkaline phosphatase and a normal LAP. Of 102 cirrhotic patients, 55% had elevated serum LAP and 29% elevated alkaline phosphatase. In a group with miscellaneous liver disease such as infectious mononucleosis, anicteric hepatitis, and granulomatosis, serum LAP and alkaline phosphatase were increased in 88% and 70%, respectively. The LAP and alkaline phosphatase were elevated in 24 and 11 patients, respectively, of 25 with choledocholithiasis and in 9 and 6 of 56 with acute or chronic cholecystitis. Elevations were noted in 26% and 34%, respectively, of patients with acute or chronic pancreatitis.

In a series of patients with benign disease not involving the hepatobiliary-pancreatic system, serum LAP was uniformly normal, but alkaline phosphatase was elevated in those with disease of the bone and malabsorption. In a variety of other diseases, the levels of both enzymes showed an irregular pattern, but concomitant LAP and alkaline phosphatase elevations were found in only 12 of 731 patients. In

(3) Ann Int Med 61 50-55, July, 1964

170 patients with cancer not known to involve the liver, serum LAP was abnormal in 6% and alkaline phosphatase in 19%. In patients with malignant lymphoma, both enzymes were abnormal with an incidence of about 25%; concomitant abnormalities were found in 13%.

The LAP test is thus a sensitive indicator of hepatobiliary tract disease and is more specific than the alkaline phosphatase test for hepatic disorders. When both tests are positive in anicteric patients, the likelihood of hepatic or biliary disease is very high.

▶ [In a companion article, a group from the same laboratory states that serial measurements of serum LAP and γ-glutamyl transpeptidase activity were more useful in detecting liver metastases than were the BSP retention test, alkaline phosphatase and GOT levels. It is unfortunate, however, that these excellent results are not substantiated by a few figures. What are the normal levels as defined by these authors? In neither article is a single value of this type given. Nor is there a statistical analysis giving the range within which 95% of all normal values would be expected to fall. Nor is the degree of abnormality in the patients with anicteric hepatobiliary tract disease given. If, for example, the values in a large number of these patients fell within the range of the normal mean ±2 standard deviations, the enthusiasm for LAP manifested in these articles would hardly be warranted.—Ed.]

Observer Variation in Endoscopic Diagnosis of Esophageal Varices: Prospective Investigation of Diagnostic Validity of Esophagoscopy. Harold O. Conn, Howard W. Smith and Murray Brodoff[4] (Yale Univ.) compared the independent findings of two experienced endoscopists in 40 patients with histologically demonstrated hepatic cirrhosis. The endoscopists, who were unaware of the patients' histories, clinical diagnoses and x-ray findings, examined the esophagus for varices sequentially during one esophagoscopy without communicating their observations to each other. Varices were reported as present or absent. Radiologic examination of the esophagus was performed on the same day in most and within a few days in all patients.

Endoscopist A made the diagnosis of esophageal varices in 19 patients (49%) and Endoscopist B in 16 (41%). Esophageal varices were found radiologically in 14 (36%). The endoscopists agreed with each other's diagnosis in 26 cases (67%) and disagreed in 13 (33%). In 11 of the 26 concurrences (42%), both endoscopists detected varices; in 15 they agreed that varices were not present.

Endoscopist A found varices in 8 patients in whom B found none, whereas B found 5 not detected by A. In most of these

patients, the endoscopist not finding varices reported prominent mucosal folds. Endoscopist A agreed with the radiologic diagnosis in 24 cases (62%) and B in 29 (74%). The barium contrast examinations of the esophagus gave the same findings in 20 (77%) of the 26 patients in whom the endoscopic diagnoses concurred.

No absolute criterion exists for determining whether or not esophageal varices are present: the barium esophagogram, esophagoscopy, splenoportography and even postmortem examinations fail to show varices demonstrable by one or more of the other methods. Further, error among a number of observers ranges from 20 to 35% in many fields of medicine. These facts should not detract, however, from the value of esophagoscopy in the diagnosis of esophageal varices. In about half the patients, the varices are sufficiently prominent to permit unanimous radiologic and endoscopic diagnoses In the case of small varices, their differentiation from prominent mucosal folds presents a major problem, which appears to be particularly prevalent in patients who have had portasystemic anastomoses.

► [In a study of 60 patients with documented liver disease, L Green and his associates (Am J Digest Dis 10 284, 1965) found esophagogastroscopy much more sensitive in identifying varices than measurement of splenic pulp pressure and splenoportography The standards in this series were the esophagogastroscopic findings, but the results, while they suggest that this technic is indeed sensitive, do not necessarily define its accuracy —Ed]

Hepatic Hydrothorax: Studies to Determine Source of Fluid and Report of 13 Cases. The incidence of hydrothorax associated with cirrhosis and not attributable to pulmonary, cardiac or pleural disease has been reported in a range of 0.4 to 10%. In a retrospective review of 200 consecutive patients with a diagnosis of hepatic cirrhosis, Robert F. Johnston and Rodolfo V. Loo[5] found 8 cases of right pleural effusion, 2 of left pleural effusion and 2 of bilateral effusion, giving an incidence of 6% of hydrothorax in this series.

Special studies were carried out in 1 patient. Comparison of pleural and peritoneal fluids obtained simultaneously revealed about equal values for electrolyte concentrations, glucose, urea and total protein. However, total cholesterol and total lipids appeared to be somewhat higher in the pleural than in the peritoneal fluid. After intraperitoneal injection of India ink, smears prepared from pleural fluid showed macrophages containing many carbon particles. At this time

(5) Ann Int Med 61 385-401, September, 1964

there were no carbon particles in smears of peripheral blood. After intrapleural injection of ink, however, there was no evidence of increased carbon particles in peritoneal fluid macrophages. Roentgenograms taken after intraperitoneal injection of carbon dioxide showed no gas appearing in the pleural space.

After intravenous injection of radioiodinated serum albumin, radioactivity appeared more rapidly in peritoneal than in pleural fluid. At 26 hours, plasma radioactivity was 1.6 times that of peritoneal fluid but 4.7 times that of pleural fluid. After intraperitoneal injection of radioiodinated serum albumin, radioactivity appeared in pleural fluid and plasma at about the same time and same concentration, indicating that radioactive iodine-tagged albumin was entering the right pleural space directly from the peritoneal cavity. However, when radioiodinated serum albumin was injected in the right pleural space, radioactivity appeared more rapidly in higher concentration in the plasma than in the peritoneal fluid, suggesting that radioactivity moved from the pleural to the peritoneal space via the plasma.

Although hypoalbuminemia and increased pressure in the azygous system because of portasystemic collaterals may play a role in the formation of the hydrothorax associated with cirrhosis, most pleural fluid is likely derived directly from the peritoneal cavity. This idea is consistent with the fact that the vast majority of patients with hydrothorax secondary to cirrhosis also have ascites. The fluid could pass from one cavity to another either through a defect in the diaphragm or via the lymphatics, but the studies here reported, showing that the two fluids were not identical, that India ink particles moved only one way and that gas did not pass from the peritoneal to the pleural cavity, all argue strongly against the presence of a defect in the diaphragm and implicate passage via the lymphatics.

Reported experiments indicate that fluid is removed from the peritoneal cavity almost exclusively by the subdiaphragmatic lymphatics. The lymph then passes from the diaphragmatic nodes into collecting ducts, which run on both sides of the sternum until they reach the anterior mediastinal nodes. From here lymph vessels probably enter the right subclavian or jugular veins. In dogs it has been found that 80% of graphite injected into the peritoneal space is carried to the

blood stream via diaphragmatic and retrosternal lymphatics In man it is likely that similar lymphatic drainage of the peritoneal cavity takes place, and this concept is supported by the finding that the lipid content of pleural fluid exceeded that of peritoneal fluid, as would be expected if there had been some dilution of peritoneal fluid with lymph. Possibly more lymphatics on the right diaphragm than on the left explains the predominance of right-sided effusions. Finally, to explain why some patients with ascites have hydrothorax and others do not, the determining factor may be variation in the rate of absorption of pleural fluid.

► [These studies on the whole confirm the importance of the lymphatic transdiaphragmatic pathway for the passage of peritoneal fluid to the pleural cavity On the other hand, they do not exclude other routes in other patients In some patients, there is a defect in the diaphragm, and gas injected into the peritoneal cavity during the days when pneumoperitoneum was a popular treatment of pulmonary tuberculosis was occasionally found in the pleural space as well In addition, although uncommon, patients with cirrhosis are observed who have repeated accumulations of fluid in the right pleural cavity in the absence of any ascites that can be detected clinically or by tap —Ed.]

Blood Ammonia during Bleeding from Esophageal Varices in Patients with Hepatosplenic Schistosomiasis was measured by Kenneth S. Warren and Gilberto Rebouças[6] (Nat'l Inst. of Health) in an effort to explain why hepatic coma is rarely seen in these patients. The 8 patients studied were considered to have compensated hepatosplenic schistosomiasis in that they had hepatosplenomegaly and esophageal varices and were infested with Schistosoma mansoni, but they did not have ascites, edema, jaundice or other indications of chronic liver disease.

Ammonia concentrations of arterial and venous blood during episodes of bleeding from esophageal varices were within normal limits or only moderately elevated. The average arterial ammonia concentration in these patients was 120 μg./100 ml. during bleeding episodes as compared with an average of 73 μg./100 ml. in 10 fasting normal subjects. Moreover, in 4 of these patients, ammonia concentrations during bleeding increased over values obtained during non-bleeding periods by only 10-15 μg./100 ml.

Two patients with repeated and extensive bleeding from esophageal varices were studied extensively. Both eventually died after portacaval shunts performed because of continued severe bleeding, death in 1 case being preceded by deep

(6) New England J Med 271 921 926, Oct 29, 1964

coma and in the other, by anuria. Early in their course when they were in a relatively stable condition, they were given three tests designed to evaluate their ammonia tolerance. (1) Ammonium chloride, 3 Gm., was given by mouth, and blood samples were taken 45 minutes later. One patient responded normally, and the other showed moderately abnormal results in that the arterial blood ammonia concentration rose from the fasting level of 98 μg./100 ml. to 168 μg./100 ml. (2) Chronic ammonia tolerance was tested by giving a diet containing 120 Gm. protein plus 2 Gm. of enteric-coated ammonium chloride 4 times a day for 5 days. In neither case did the venous blood ammonia, sampled at various times during the 5th day, exceed 104 μg./100 ml. (3) Finally, an intravenous infusion of ammonium chloride was given. The results were similar to those obtained in normal subjects.

Electroencephalograms made when these 2 patients were in a stable condition showed mild abnormalities which were not changed by either the ammonium tolerance tests or a morphine tolerance test. No neurologic or psychologic abnormalities, moreover, were observed during any of these procedures.

In the patient who eventually died in hepatic coma, blood ammonia levels rose markedly (arterial concentration 326 μg./100 ml.) just before death. In 3 other patients categorized as having decompensated hepatosplenic schistosomiasis with ascites and other signs of chronic liver disease, episodes of bleeding esophageal varices were attended by moderate to marked rises in blood ammonia levels.

Many patients with hepatosplenic schistosomiasis have excellent liver function in the presence of extensive portosystemic collateral circulation. When varices in such patients rupture and bleed, the patients do not tend to show signs of hepatic coma, nor are they unduly intolerant of ammonia or ammonia precursors, whether given orally or parenterally. Consequently, the concept that elevated blood ammonia levels occurring during episodes of upper gastrointestinal bleeding in patients with esophageal varices are due primarily to shunting of blood around the liver appears to be erroneous. Patients with bleeding esophageal varices but good liver function can maintain normal blood ammonia concentrations. A corollary of this conclusion is that the blood ammonia level is not a good test for identifying the site

of upper gastrointestinal bleeding in patients with good liver function.

Idiopathic and Bantu Hemochromatosis. A comparative histologic study was carried out by T. H. Bothwell, C. Abrahams, B A. Bradlow and R. W. Charlton[7] (Univ. of Witwatersrand) to determine whether any criteria existed whereby these two forms of hemochromatosis might be differentiated. Hepatic sections believed to represent idiopathic hemochromatosis were taken from 13 white subjects, 11 of whom were male. All had skin pigmentation and hepatomegaly, 5 were diabetic, and 4 died of cardiac complications. Deposits of iron were prominent in a number of organs other than the liver No patient took alcohol excessively, nor was there any obvious source of excessive dietary intake of iron.

Bantu hemochromatosis was represented by hepatic sections taken from 13 Bantu patients, 11 males, all of whom had advanced hepatic siderosis and portal cirrhosis. There was good evidence, although incomplete, that these patients had had long exposure to various local alcoholic beverages, and previous studies had indicated that the male Bantu may ingest 50-100 mg. iron daily in such beverages

The amount of hepatic iron deposits was graded separately on a 0-3+ scale in parenchymal cells, Kupffer cells, portal tract phagocytes and bile duct epithelium. The mean relative values of hemosiderin distributions at these four sites were, respectively, as follows (the rating for idiopathic hemochromatosis is the first figure in each ratio): 3.0:2.0; 1.8:2.9, 1 3:3.1; and 1 9:1 3. Thus, stainable iron was found predominantly in the parenchymal cells in idiopathic hemochromatosis, whereas these deposits were primarily in the Kupffer cells and portal tracts in Bantu hemochromatosis (Figs. 70 and 71). These differences were sufficiently marked that an independent pathologist, who examined all samples "blind," was able to separate the two groups with complete accuracy Also, comparison of splenic sections from 7 white patients with 4 obtained from Bantus showed a mean ratio of iron deposits of 0.6:2.8.

These studies do not support the hypothesis that hemochromatosis is only a variant of nutritional cirrhosis occurring in patients also exposed to excessive iron To the contrary, it seems that prolonged ingestion of alcohol with a

(7) Arch Path 79 163-168 February 1965

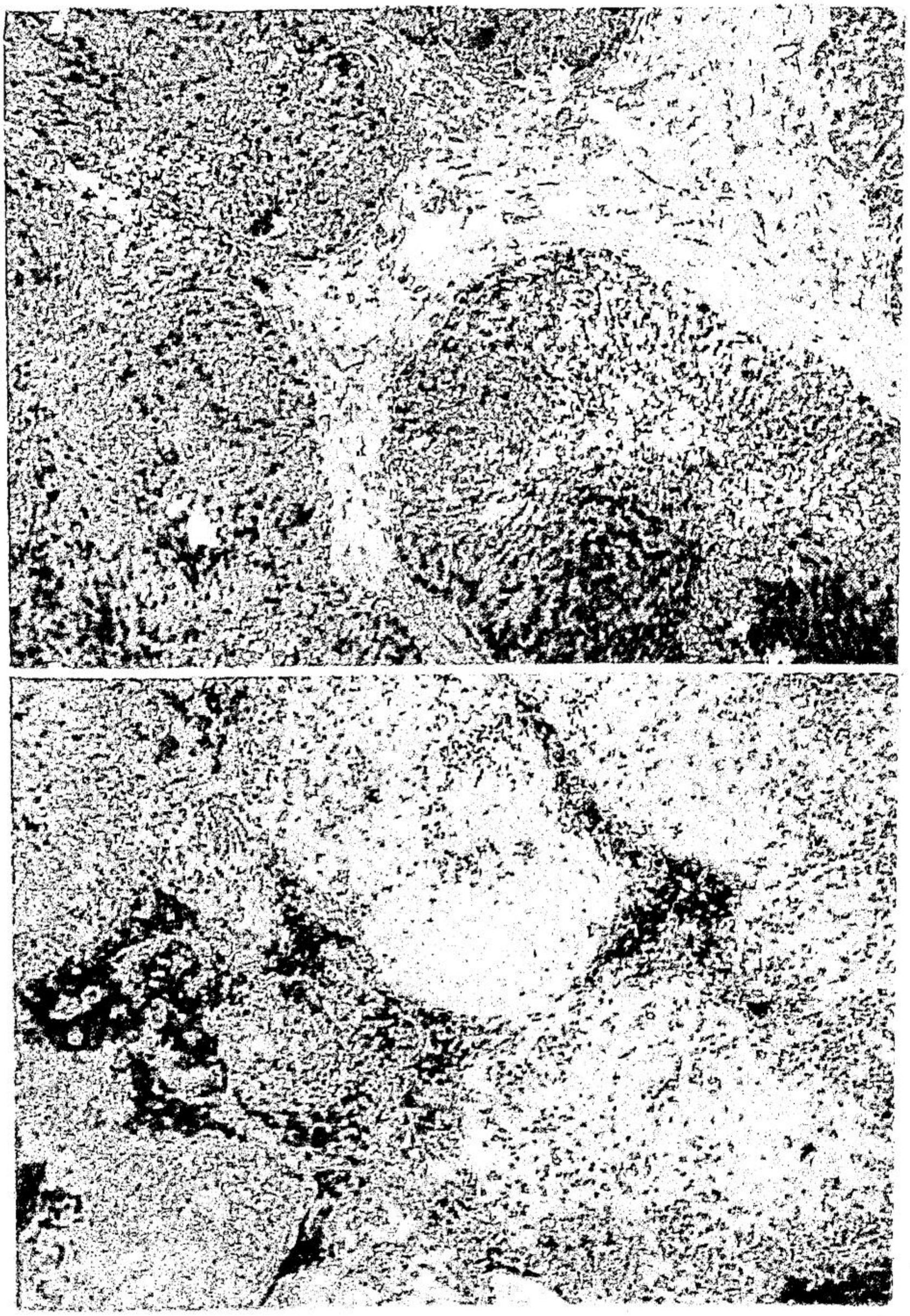


Fig. 7 (top).—Section of liver from patient with idiopathic hemochromatosis showing increased iron in Lemsidemn granules in parenchymal cells with relatively little iron in portal tracts and fibrous tissue. Perls stain ×250.

Fig. 7 (bottom).—Section of liver from Bantu patient with hemochromatosis showing intense accumulation of Lemsidemn granules in portal tracts and fibrous tissue and moderate increase in parenchymal cells. Perls stain ×250.

(Courtesy of Bothwell, T. H., *et al.*: Arch. Path. 69:103-108, February 1960.)

high-iron content, together with a possibly suboptimal diet, results in a hemochromatosis morphologically distinct from idiopathic hemochromatosis. The cause of the different distribution of iron in the idiopathic disease, however, is not known. Perhaps some alteration in reticuloendothelial function prevents conspicuous iron deposits in the reticuloendothelial cells of the liver and spleen of those who have the idiopathic type. Alternatively, the different distribution of iron deposits may reflect other factors, such as more active liver disease in the Bantu with constant release of iron from necrosing liver cells into the reticuloendothelial system However, the exact cellular localization of iron in different types of iron overload must be precisely specified if meaningful debates are to occur between workers holding different theories concerning pathogenesis of hemochromatosis

Hepatolenticular Degeneration (Wilson's Disease): Two Different Components are described by Derek Denny-Brown[8] (Harvard Med. School), whose 14 years' experience led him to conclude that the two types of cerebral symptomatology described by Westphal and Wilson react differently to treatment with chelating agents such as BAL, versene and penicillamine.

The Westphal pseudosclerotic variety begins between ages of 19 and 35, and characteristic defects are tremor and dysarthria. There is a flapping tremor of the wrists with "wing beating" at the shoulders, particularly when the arms are flexed and the shoulders abducted. The dysarthria is slurring, but with a tendency to scan. Dystonic fixity of posture is not a feature, although some patients exhibit a fixity of facial expression and infrequency of blinking. The untreated disease is only slowly progressive. Cirrhosis is invariably present, usually with no evidence of any hepatic disorder until ascites appears.

Progressive lenticular degeneration as described by Wilson begins between ages of 7 and 15, and a history of hepatic symptoms in the patient or other members of the family is common. The first signs are apt to be dystonic with abnormal postures of limbs when they are outstretched or in walking. Facial expression is set. A rapid tremor of the fingers may be seen, but the flapping tremor develops late, if at all. As the condition worsens, athetoid movements may herald onset of

(8) New England J. Med. 270 1149-1156, May 28, 1964

fixed dystonic postures. Ultimately the limbs become continuously overflexed in a posture called "hemiplegic dystonia." Mental disorders including psychoses may be early symptoms. Progression of the disease, though irregular, is usually rapid, survival over 4 years being rare without treatment.

Patients with the pseudosclerotic, adult type of disease responded on the whole satisfactorily to treatment, particularly with respect to neurologic symptoms. In patients who died, cirrhosis of the liver, rather than neurologic disease, appeared to be responsible. In contrast, results in the juvenile form described by Wilson have been uniformly disappointing, although there were some temporary remissions. In particular, primary dystonic attitudes of the limbs indicate a poor prognosis. In contrast, flapping tremors, even if associated with some dystonia, predict a better response to treatment.

It appears certain that the liver proteins of patients with Wilson's disease have an enormous affinity for copper and some defect in protein synthesis must underlie this affinity. A similar affinity for copper is not necessarily present in cerebral protein. Thus the liver damage is often slowly progressive and does not respond satisfactorily to chelation therapy, but in the adult, pseudosclerotic type of Wilson's disease, the copper that has accumulated in the nervous system does respond. In young patients with dystonia, there is evidence that the central nervous system damage is not related directly to the accumulation of metallic copper, but rather represents the effects of some noxious factor of hepatic origin, possibly related to the abnormal protein synthesis that underlies the disease. Chelation in such cases is therefore not effective. Since the mechanisms responsible for the symptoms and the specific role of copper are still so uncertain, there is no need for relentless chelation therapy in patients who do not have signs of progressive hepatic or neurologic damage.

Penicillamine Therapy for Hepatolenticular Degeneration is evaluated by Irmin Sternlieb and I. Herbert Scheinberg[9] (Albert Einstein College of Medicine) on the basis of experience with this treatment in 33 patients. Eight patients were asymptomatic but had hypoceruloplasminemia and in-

[9] J.A.M.A. 189:748-754, Sept. 7, 1964.

creased hepatic copper concentration. Therapy aimed to promote excretion of copper and to minimize absorption of dietary copper. To promote copper excretion, penicillamine was given in divided oral doses totaling 1-4 Gm daily, with D-penicillamine being used since 1960. The patients were given a low-copper diet, excluding liver, chocolate, cocoa, nuts, mushrooms, shellfish, brain, molasses, broccoli and cereals enriched with copper, and they were given 40 mg potassium sulfide with each meal. Progress was evaluated clinically, by slit-lamp inspection of the cornea, by measurement of 24-hour urinary copper excretion and by determination of ceruloplasmin and copper levels in the serum.

Of the 25 symptomatic patients, 6 died, but in only 1 was death directly related to central nervous system damage Two deaths were due to hepatic failure, 2 patients died postoperatively and 1 died of an unrelated cause. Four patients who had such severe neurologic manifestations as to be bedridden and completely incapacitated underwent dramatic improvement, so that 3 could eventually lead nearly normal lives. Variable improvement of neurologic symptoms was also observed in the other patients, except in 2 who had irreversible damage to the cerebral tissues. Improvement, however, did not always start promptly on initiation of penicillamine treatment; indeed, in 4 patients tremors transiently became worse, but temporary interruption of therapy followed by readministration of penicillamine was subsequently attended by improvement.

Psychiatric disturbances preceded other signs of hepatolenticular degeneration in 5 patients and appeared simultaneously with neurologic hepatic disorders in another 8 Although variable degrees of improvement were achieved by penicillamine therapy in three fourths of these patients, psychiatric manifestations did not respond as well as neurologic symptoms to chelation.

Direct evidence of liver disease or indirect effects, such as hypersplenism, leukopenia or thrombocytopenia, were common. Indeed, all 25 symptomatic patients had clinical and laboratory abnormalities indicating hepatic dysfunction. By and large these hepatic disorders responded rather poorly to penicillamine, but among patients who had repeated liver biopsies, hepatic copper concentration decreased in 5, in others hepatic fibrosis decreased somewhat, and in 2 patients

diffuse fatty infiltration disappeared from the liver. Splenomegaly, when present, did not change in any patient.

Kayser-Fleischer rings, present in 25 patients before therapy, diminished noticeably in 7 and disappeared in 9 others. Rings did not develop in 8 of the asymptomatic patients who were treated.

Concentrations of serum ceruloplasmin, which were extremely low in most of the patients, changed but little or inconsistently. Total serum copper decreased erratically in most patients. Urinary copper excretion decreased progressively with treatment in all patients.

A number of toxic effects of penicillamine were noted. Acute sensitivity reactions characterized by skin rashes and fever occurred during the first 4 weeks of treatment in 6 patients. Prolonged administration for over a year was associated in 6 with extravasations of blood into the skin, particularly at sites subject to pressure or trauma. In 5 patients leukopenia followed administration of penicillamine, and 3 patients had thrombocytopenia. Both these hematologic complications subsided after discontinuance of therapy. As a general rule sensitivity reactions were readily overcome by temporarily discontinuing treatment or, if necessary, adding prednisone. Other side effects such as gastrointestinal pain, iron deficiency and vitamin deficiency were mild and could be corrected by appropriate therapy. A nephrotic syndrome, reported by others, was not observed in this series.

These results support the belief that patients with a diagnosis of Wilson's disease should be treated vigorously and indefinitely, and that such treatment should be given not only to those with clinical symptoms but to those in whom a diagnosis is made on the basis of the biochemical criteria of ceruloplasmin deficiency and increase of hepatic copper. Some patients will not respond because of advanced and irreversible changes. Patients who will prove refractory to treatment cannot, however, be detected in advance of therapy, and some of the most dystonic persons have had the most dramatic responses to treatment. Thus the classification of the disease into juvenile and adult forms, which has some clinical and pathologic use, has little bearing on prognosis for patients treated with penicillamine

► Is it not remarkable that controversy is so rife with respect to the pigment cirrhoses, hemochromatosis and Wilson's disease? In both conditions, the pathogenetic mechanisms are hotly debated and, correspondingly, the thera-

peutic standard of one camp is the abhorrence of the other. Purge the body of those metals persistently and, if necessary, prophylactically is the cry of one side, whereas the other disparages this attack on what they consider merely a secondary involvement of copper or iron.

Few who are not expert would dare strongly to support one side or the other, but those who incriminate a defect in copper metabolism as the primary difficulty at least have a more concrete foe than those who would contend with a completely hypothetic hepatic dysfunction.—Ed.]

Studies with Radiocopper (Cu^{64}) in Wilson's Disease: Liver-Thigh Ratio. S. B. Osborn and J. M. Walshe[1] studied 9 controls, 3 parents of patients with Wilson's disease and 10 patients with Wilson's disease to assess their rates of hepatic copper uptake. Between 48 and 134 μc. Cu^{64} was injected intravenously. Uptake by the liver of radioactivity was measured by a scintillation counting apparatus, which had been calibrated on the basis of model livers of various sizes. Since apparent liver radioactivity uptake could be caused by blood circulating through the liver as well as by radioactivity in hepatic parenchymal cells, radioactivity over the thigh was also counted in order to assess radioactivity in circulating blood.

In all subjects, radioactivity in the liver increased rapidly after injection of Cu^{64}, and this initial radioactivity could be largely attributed to blood circulating through the liver. With time, however, radioactivity in the liver gradually increased and that over the thigh decreased in normal subjects. As a result, the ratio of liver and thigh counts in the normal subjects rose progressively, with mean values of 2.2 (range 1.7-2.4), 4.8 and 7.2 at 15 minutes, 4 hours and 24 hours, respectively, after Cu^{64} injection.

In the patients with Wilson's disease, the pattern was quite different. After the initial peak of radioactivity, hepatic counts gradually decreased, so that the liver-thigh ratio tended to hover about 1 and did not overlap with the ratios found in the controls. Mean liver-thigh ratios in the patients with Wilson's disease were 0.8 (range 0.5-1.2) at 15 minutes, 1.4 at 2 hours and 1.6 at 24 hours. In the 3 subjects heterozygous for the Wilson's disease gene, the liver-thigh ratios fell clearly in the normal range. The liver-thigh ratio may therefore be used for diagnosis of Wilson's disease and will separate homozygous abnormal subjects from heterozygous persons. Other types of liver disease, such as juvenile cirrhosis, however, present a problem, and the results of

(1) Clin. Sc. 27: 319-328, October, 1964

injecting Cu^{64} in patients with such conditions and determining the liver-thigh ratio require further study.

Besides their diagnostic value, the results obtained indicate that the liver in patients with Wilson's disease does not have, as has been claimed, an increased avidity for copper. To the contrary, hepatic uptake is impaired, supporting the hypothesis that the primary defect in Wilson's disease is the absence of hepatic enzymes needed for uptake of copper from plasma and possibly also for its incorporation into ceruloplasmin.

► [In a personal communication, the authors aver that the injected copper salt is not in colloidal form in the blood and that no evidence exists for its uptake by Kupffer as opposed to polygonal cells —Ed.]

THE GALLBLADDER AND PANCREAS

Clinical Implications of Physicochemical Studies on Bile Salts are reviewed by Alan F. Hofmann[2] (Rockefeller Inst.). Bile salts are anionic detergents which exist in aqueous solution in two phases: as dispersed, unassociated molecules and as macromolecular aggregates known as micelles. Micelles are not present in dilute solutions but form when the concentration of bile salts reaches a level called the critical micellar concentration. Temperature also affects micelle formation critically, the temperature at which micelle formation begins being called the Krafft point. Under physiologic conditions prevailing in the biliary system and intestine, the concentration of bile salts is well above the critical micellar concentration and the temperature exceeds the Krafft point. Therefore, under such conditions, bile salts are always in micellar solution.

Compounds able to form micelles are known as amphipathic, i.e., possessing two kinds of "feelings," one with sympathy, the other with antipathy to water. Thus amphipaths have appropriately arranged polar, hydrophilic regions and nonpolar, hydrophobic, lipid soluble regions. In general, the larger the hydrophobic moiety, the lower the critical micellar concentration.

[2] Gastroenterology 49:484-494, April, 1965.

Under physiologic conditions, bile salt micelles are roughly spherical, but cylindrical and lamellar aggregates may form if bile salt concentration is unnaturally increased. Whatever the form of the micelle, it is in constant equilibrium with unassociated molecules dispersed in the solvent. This is of considerable importance in interpreting a variety of experiments. If bile is dialyzed, for example, the unassociated bile salt molecules will first pass across the membrane, and ultimately the entire solution will pass through the membrane since the unassociated molecules are in equilibrium with the micellar molecules. This equilibrium of micelles with their unassociated components differentiates them from lipoprotein macromolecules.

Micelles are thought of as containing bile salts so arranged that their polar, water-soluble, negatively charged ends point outward, whereas their lipid soluble regions are oriented toward the center of the micelle. This micellar structure permits the solubilization of lipid solutes, a phenomenon known as micellar solubilization. Two types of micellar solutes are recognized. One is a nonpolar solute, such as a hydrocarbon, and it may be regarded as dissolved in the lipid core of the micelle. The second is termed a polar solute and involves a substance, a portion of which is hydrophilic. When a polar solute is solubilized in a micelle, the hydrophilic region of the solute molecules is oriented between the radially arranged bile salt molecules so that the solute polar ends are also facing outward. These concepts, however, are highly schematized, and a purely spherical micellar form containing a polar solute probably does not exist.

In bile, the bile salt concentration is 100-300 mM., and the free taurine and free glycine conjugates that make up human bile salts exist in micellar solution in bile and in the intestine. Important differences between these conjugates have not been clearly shown. Cholesterol, which behaves as a nonpolar solute in spite of its hydroxy group, is probably held in solution at the hydrophobic core of the micelle. The ability of human bile to solvate cholesterol, is, however, greatly increased by the fact that lecithin is present to act as a component of the micelle in the form of a polar solute, for lecithin has a polar end although by itself it is quite insoluble in water.

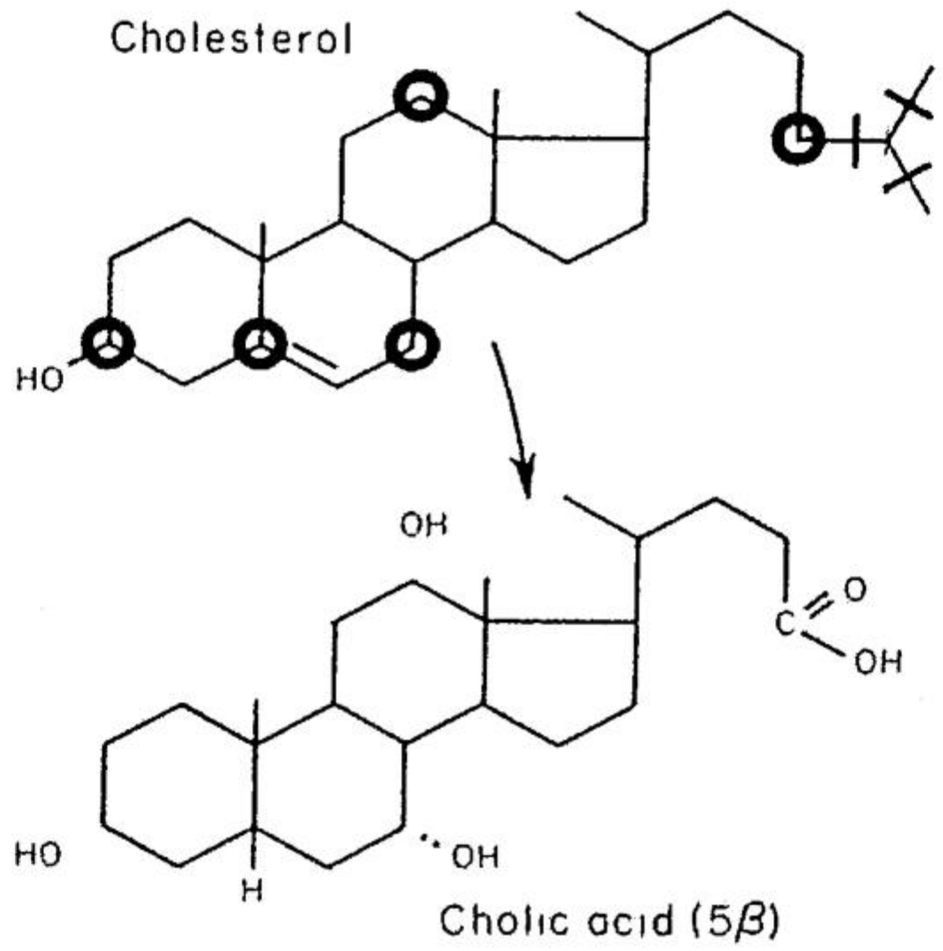


Fig 72 1 - Conventional representation of conversion of cholesterol into colic acid Circles indicate positions where chemical changes occur during transformation When depicted in this manner, the difference in steric configuration between precursor and product is not apparent (Courtesy of Hofmann, A F Gastroenterology 48 484 494, April, 1965)

The exterior of the micelle presents many negative charges. Some of these charges hold anions in a "bound" form in which they cannot exert their usual electric and osmotic activity. Because of these bound ions, the formation of micelles permits a high concentration of substances to be dissolved in bile without increasing the osmotic pressure above isotonic range. For this reason, much less osmotic work is required to produce concentrated gallbladder bile (up to 300 mM.). On the other hand, a substance such as dehydrocholic acid (Decholin), which is an unconjugated and unoxidized bile acid with no amphipathic properties, produces a marked flow of bile in a fashion analogous to the production of an osmotic diuresis by an appropriate solute excreted by the kidney.

Micelles bind calcium ions even more strongly than sodium ions. Hence, bile appears to be composed of a solution containing micelles composed of bile salt, lecithin, cholesterol, calcium and sodium. Perhaps some protein is adsorbed on the surface. Whether bile pigments are part of the micelle is unknown.

In spite of high concentration of calcium in bile, calcium salts of bile acids rarely precipitate from bile in man. This resistance to the formation of insoluble calcium bile salts depends crucially on the molecular structure of natural bile

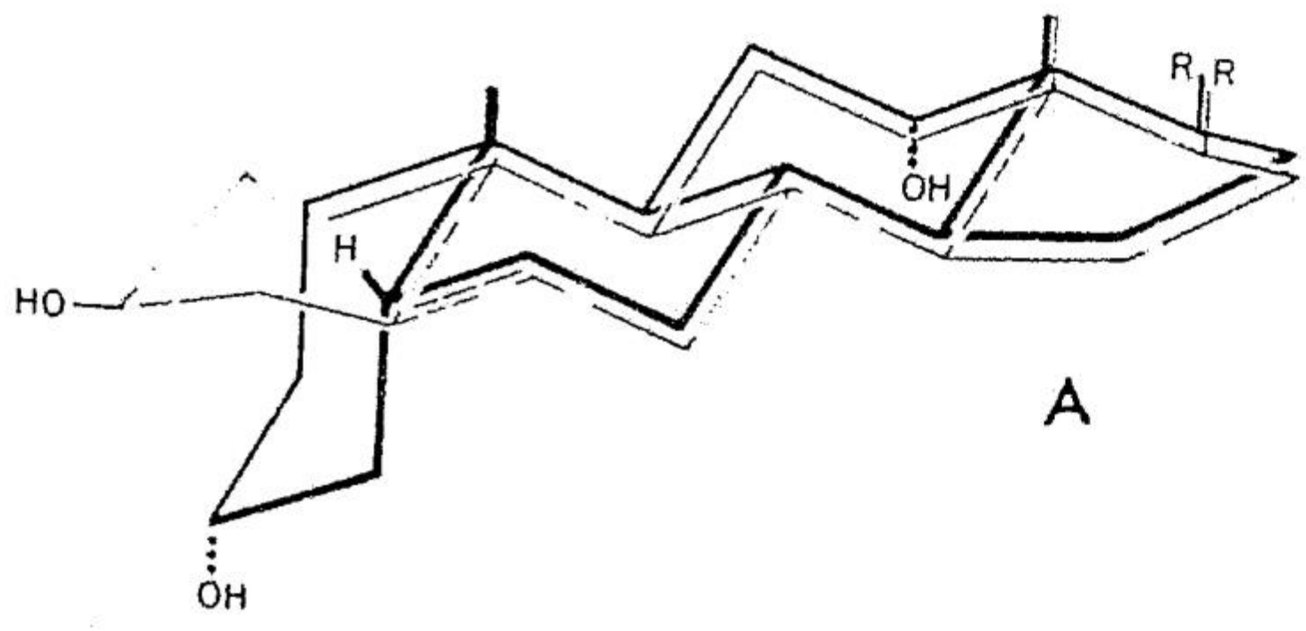


Fig 72-2 —Perspective representation of conversion of cholesterol into cholic acid The precursor is shown in front and is drawn in fainter lines than the product A, conversion of cholesterol to cholic acid (5β, A B *cis*) in the normal animal The striking change in steric configuration of precursor and product is evident The flat cholesterol molecule is trans formed into an L shaped bile salt molecule when its Δ^{-6} double bond is saturated stereo specifically B conversion of cholestanol into an allo-(5α, A/B *trans*) bile acid in the cholestanol-fed rabbit The unnatural precursor has no double bond, and the product keeps the same flat shape as its precursor It forms insoluble calcium salts, and precipitates from solution in the form of biliary calculi (Courtesy of Hofmann, A F Gastroenterology 48 484–494 April, 1965)

salts and is lost if the steric configuration of bile salts is changed. For example, conversion of cholesterol to cholic acid (5β) requires saturation of the 5-6 double bond with a *cis* position of the hydroxyl group and with a kinked configuration at the junction of the A and B rings (Figs. 72-1 and 72-2). This normal configuration promotes the formation of micellar solutions. When a *trans* or allo-bile acid is present, however, it readily links with calcium to precipitate as an insoluble calcium soap.

► [It is hard to imagine a more fact-full presentation concerning the physical chemistry of bile and bile salts, and yet the story is lucidly told and can be enjoyed by the man who has little biochemical or biophysical training It is fully equal to many of the articles that have appeared in the *Scientific American*, and both author and journal have a right to feel proud.

In addition to the material abstracted, Doctor Hofmann's review contains a description of the micellar phase in the intestinal contents, but this portion of his review has been purposely omitted here —Ed]

Identification of Allodeoxycholic Acid as Major Component of Gallstones Induced in the Rabbit by 5α-Cholestan-3β-OL. Normally, unsaturated cholesterol is converted to bile acids by the stereo-specific introduction of hydrogen in the 5β configuration with an A/B ring juncture that is *cis* A satu-

rated homologous compound with the 5 hydrogen in an alpha configuration is known as cholestanol. When cholestanol is fed to rabbits the *trans* A/B ring structure is maintained, and 5α bile acids are formed. Bile acids with an alpha configuration are known as allobile acids. The feeding of cholestanol to rabbits, moreover, produces inflammation of the biliary passages and gallstones, and chemical and isotopic studies have shown that the stones which form principally contain bile acid derived from cholestanol. Alan F. Hofmann and Erwin H. Mosbach (New York) succeeded in further identifying the nature of the gallstones formed under such experimental circumstances.

Gallstones from rabbits fed cholestanol were analyzed by various procedures. The major bile acid constituent was found to be 3α, 12α dihydroxy-5α-cholanic acid, i.e., allodeoxycholic acid. The principal cations present in the gallstones were calcium, sodium, and potassium, which were present, in terms of molar percentage, in a ratio of 51:41:8.

Deoxycholic acid is not formed in the liver in the rabbit, but by bacterial removal of a 7α-hydroxy group from cholic acid in the intestine. The studies suggest that intestinal bacteria can also remove a hydroxy group from the unnatural allocholic acid and that the resulting allodeoxycholic acid can be absorbed and then re-excreted by the liver.

The formation of gallstones with allodeoxycholic acid can be explained because this substance, in the presence of calcium and sodium ions, forms an insoluble calcium salt at far lower calcium concentrations than normal glycodeoxycholic acid.

[The relation of this article to the immediately preceding one is obvious. In addition, as the authors point out, a new biochemical syndrome based on stereo-isomerism appears to be developing. Eating a stereo-isomer of cholesterol produces gallstones in the rabbit; and in man, etiocholanolone fever is produced since some persons form abnormal stereo-isomer, 5β-androsterone.

More recently, Robert H. Palmer has reported that rats fed lithocholic acid consistently form gallstones in the gallbladder (Science 148.1339, 1965). Lithocholic acid, although not an allo-bile acid, is a monohydroxy bile acid which is not the result of normal hepatic synthesis in man but may form in the intestine as a result of bacterial action. They glycine conjugate of lithocholic acid readily forms insoluble calcium salts not only in the gallbladder but also in the hepatic ducts of the rat. These studies, as well as those reported by Hofmann and Mosbach, indicate how delicately crucial the normal bile acid structure is for maintaining bile free of potentially stone-forming precipitation. —Ed.]

(3) J. Biol. Chem. 239:2013-2021, Sept., 1964.

Sequelae Attributed to Delayed Surgical Treatment of Gallstones. C. Elton Cahow, Jr., and Frank Glenn[4] (New York Hosp.-Cornell Med. Center) followed two groups of 35 women each, all of whom had had one or more pregnancies and had been operated on for acute cholecystitis with cholelithiasis

The women in group I had been operated on between ages 21 and 30 Twenty-nine had had only cholecystectomy and were examined 1-26 years later, 27 had no symptoms suggesting biliary tract disease, but 2 had symptoms possibly related to this tract. Thus results were good in 93%.

Six patients had had cholecystectomy and choledochotomy for suspected common duct calculi In 3, no stones were found, but 1 had transient symptoms later In the 3 with common duct stones, 1 required a second operation for removal of a second stone. In 91%, results were classified as good.

Group II patients had cholecystectomy between ages 60 and 75. They differed from the first group in that they had sequelae and complications of calculous biliary tract disease In addition, they had coexisting diseases, often quite severe Eighteen, who had had simple cholecystectomy, were followed for 1-23 years. Two had recurrent symptoms possibly related to biliary tract disease, resulting in 89% satisfactory results. Six patients had choledochotomy as well as cholecystectomy, and 2 of these had to have subsequent operations for retained stones. In these 6 patients, followed for 1-13 years, the end result of operation was good in only 4, and 1 patient died during the second operation.

Six patients had cholecystostomy. One died 4 days after this procedure, and 3 of the 5 remaining patients had subsequent symptoms requiring subsequent cholecystectomy. All had associated disorders such as cardiovascular disease, emphysema or hiatus hernia. After cholecystectomy, however, 3 patients did well. Three other patients had complications after initial cholecystostomy; results after subsequent cholecystectomy were good. A final 2 patients had to have multiple operations on the biliary tract because of complications, but each did well after the necessary procedures.

The 92% incidence of good results in the young patients compared with 77% in the older patients supports the belief that surgical treatment interrupts the natural course of

(4) Ann Surg 161 21 26 January, 1965

calculous biliary tract disease; it indicates that when stones are limited to the gallbladder of a young woman, cholecystectomy stops the disease and prevents later complications. Whether or not symptoms are present seems to make little difference. The contention of outstanding surgeons such as Mayo, Graham, Whipple and Lahey that asymptomatic stones should be removed is even more appropriate now than in their day.

► [If soundness of reasoning and observance of scientific methods on one hand are related to the validity of the conclusions on the other, this is one of the best articles that may be found in support of never operating on the asymptomatic gallbladder – Ed.]

Exocrine Secretion from Isolated Rabbit Pancreas was studied by a new method devised by S. S. Rothman[5] (Univ. of Pennsylvania).

METHOD – The pancreatic duct was cannulated in situ, after which the entire mesomentum included in the duodenal loop extending from the gastroduodenal junction aborally 30-40 cm. was removed as a unit. The entire loop including the pancreas was then mounted and placed in a Plexiglas chamber, where it was bathed with a balanced salt solution containing, among other electrolytes, $NaHCO_3$, 24.9 mM./L. The preparation was gassed with 95% oxygen and 5% CO_2 and maintained at 30 C. (Fig. 73). Adequate oxygenation of the rabbit pancreas by this means is possible because it is only about 0.2 mm. thick.

Pancreatic secretion varied from 28 to 561 μl. per hour and was relatively constant up to 5 hours. The mean basal secretory rate in fasted animals was 303.5 μl. per hour, whereas in vivo the mean flow in a fasted anesthetized animal is only 59.4 μl. per hour. Flow from the in vitro preparation ceased if its oxygen was replaced by nitrogen or if it was exposed to sodium fluoride and sodium azide.

Pancreatic juice bicarbonate concentrations were obtained up to four times the bath bicarbonate concentration. With higher flow rates, bicarbonate concentration approximated 76-88 mM./L.; the sum of bicarbonate and chloride concentration was relatively constant with a mean of 146.1 mM./L. In situ preparations of rabbit pancreas produce juice with bicarbonate concentrations of 90-100 mM./L.

With the exception of the gastric glands, mammalian digestive glands have been studied in vitro only with the aid of tissue-sectioning technics. The technic here described offers a method for evaluating the role of various peripheral control mechanisms on pancreatic secretion. It is noteworthy

(5) Nature, London, 204:84-85, Oct. 3, 1964.

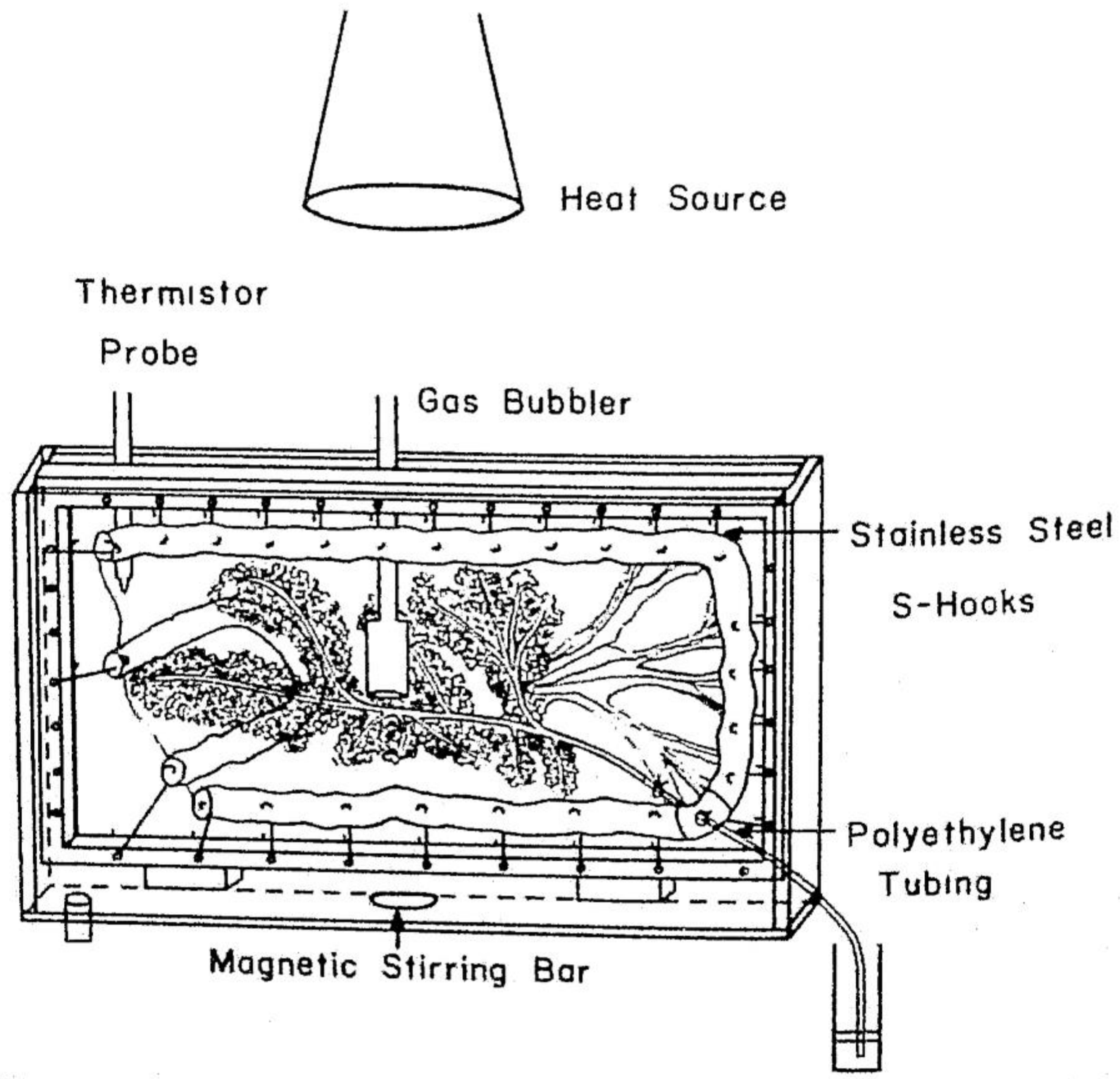


Fig. 73.—Schematic diagram of rabbit pancreas and duodenum suspended in chamber (175 ml volume) (Courtesy of Rothman, S. S. Nature, London 204: 84-85, Oct. 3, 1964.)

that the pancreas, in the absence of blood-perfusing pressure as an energy source, can secrete a fluid of volume and ionic content comparable to that found when the organ is studied in situ.

► [The pancreas thus joins other digestive organs, such as the small intestine and gallbladder, which continue to exercise their main function when deprived of their blood supply, lymph drainage and nervous control and placed in a totally unnatural environment. In such preparations, many crucial and basic aspects of transport through epithelial tissues can be analyzed, and it is tempting to assume that the results so obtained are similar to those that would be obtained if the organ were in its natural position within the body. This, however, is far from established, and probably a number of major discrepancies exist. From a theoretical viewpoint, it must be remembered that absorption from an inverted gut sac on one hand or secretion from an isolated pancreas on the other is determined by fluid and solute transfer not only across the usual epithelial and immediately subepithelial tissues but across the entire wall of an organ, including muscle, connective tissue and serosa.—Ed.]

Trypsin Release, Kinin Production and Shock were studied in experimental and human pancreatitis by W. Katz, M. Silverstein, E. E. Kobold and A. P. Thal[6] (Detroit). Experimental pancreatitis was produced in 35 dogs by injecting bile under moderate pressure into the pancreatic duct. In 10 dogs, no

(6) Arch. Surg. 89: 322-331, August, 1964.

further procedure was carried out, and their mean survival time was 17 hours. In 25, total pancreatectomy was performed at various intervals after induction of pancreatitis. Survival was not affected if the interval was 1 hour or more, but in 5 dogs pancreatectomized within 30 minutes of induction of pancreatitis, the mean survival time was 40 hours, comparable to the mean survival time of 50 hours for 3 dogs subjected to removal of a normal pancreas. This finding confirmed previous studies and suggested that a toxic substance or its precursor is formed and released during the early phase of acute experimental pancreatitis.

Trypsin was assayed by measuring the rate of hydrolytic activity of a 1-mM. solution of TAMe (a-p-toluene-sulphonyl-L-arginine methyl ester HCl). According to this method, trypsin activity greatly increased in edema fluid surrounding the acute pancreatitic process, maximum activity being present 1 hour after induction of pancreatitis. Peritoneal fluid, which developed rapidly after induction of pancreatitis, also exhibited marked tryptic activity, usually maximal within the 1st hour. The level of vasoactive polypeptides such as bradykinin (determined by bioassay) in peritoneal fluid increased more slowly, reaching a maximum at about 4 hours.

Blood taken from the pancreaticoduodenal vein during the first 30 minutes after induction of pancreatitis and then incubated had maximum bradykinin activity at about 10-15 minutes, presumably because trypsin in the plasma was liberating bradykinin from plasma α_2-globulins. This apparent early increase in proteolytic activity was inconsistent with results of the survival experiments, which showed that pancreatectomy protected dogs if performed within 30 minutes of induction of pancreatitis, but noxious substances from the pancreas may be distributed to the body by other than vascular routes once the pancreatitis is underway.

When vasoactive material was measured in the femoral, hepatic and portal veins, it was apparent that polypeptide substances, histamine and, to a lesser degree, serotonin and catecholamines, all measured by bioassay, tended to increase at 3 hours and reach maximum levels at 6 hours. Usually, between these hours, hypotension and shock tended to occur. Somewhat similar results, particularly with respect to venous polypeptide concentration, were found in human acute

pancreatitis, and, in general, the more acute the pancreatitis the higher the polypeptide levels.

The role of trypsin in acute pancreatitis is difficult to assess, particularly since a complex trypsin inhibitor system exists in blood and tissues. As indicated by the studies cited, trypsin may act in part by liberating bound stores of histamine and of hypotensive polypeptide such as bradykinin from peripancreatic tissue and from ascitic fluid. Ascitic fluid serves as an ideal medium, for it contains the α_2-globulin substrate needed for liberation of vasoactive polypeptides but does not contain much trypsin inhibitor. Although trypsin may not be absorbed as such from the peritoneal cavity, the polypeptides are rapidly absorbed and may play a role in the facial flush, plasma loss and hypotension seen in acute necrotizing pancreatitis.

► [The complex phenomena that attend pancreatitis and the various pharmacologically active substances that may be released during this disease, particularly as a result of tryptic activity, are hinted at by this report. The words "hinted at" are used advisedly, for the results are presented either as broad generalizations or in the form of individual "representative" findings. The ideas expressed must therefore be accepted as provocative but, at present at least, far from definitive.—Ed.]

Comparison of Urinary and Serum Amylase Values Following Pancreatic Stimulation in Patients with and without Pancreatic Disease was made by Robert Kirshen, Earl Gambill and Harold Mason[7] (Mayo Clinic and Found.). Vitrum secretin (100 clinical units) was given intravenously, and the effects on serum amylase levels and on urinary amylase output were determined. Urine was collected for a 2-hour period before, and for three 2-hour periods after pancreatic stimulation. Blood for amylase determinations was drawn before and at 30, 60, 90, 120 and 240 minutes after pancreatic stimulation. The data were interpreted in terms of the maximal increase over the prestimulation levels found in each subject.

The subjects studied included 23 controls; 8 patients with subacute pancreatitis (established by laparotomy in 4) studied 1-3 weeks after an acute attack; 12 patients with chronic relapsing pancreatitis who had had at least 2 attacks, the last having occurred 6 weeks to 6 months before study (laparotomy in 7); 5 patients with advanced chronic pancreatitis (laparotomy in 4) with steatorrhea; and 6 patients with surgically proved cancer of the pancreas. The mean maximal

(7) Gastroenterology 48 579 582, May, 1965

MEAN RATE OF URINARY AMYLASE EXCRETION (UNITS PER HOUR) AND MEAN SERUM AMYLASE CONCENTRATION (UNITS PER 100 ML)

Patient group	Amylase			
	Mean rate of excretion in urine		Mean serum value	
	Before stimulation	Maximal rate after stimulation[a]	Before stimulation	Maximal value after stimulation[a]
Controls	148	174	106	107
Subsiding acute pancreatitis	536	1096	299	328
Chronic relapsing pancreatitis	178	599	125	189
Pancreatic steatorrhea	154	168	71	83
Pancreatic carcinoma	224	554	118	128

[a]Highest value or rate attained in any poststimulation period

changes in amylase concentration in the serum and in amylase output in the urine in these 5 groups are shown in the table.

If the upper limit of serum amylase output in units per hour is defined as 270 (mean plus 2 standard deviations of mean), the postsecretin urinary amylase output reached maximal values exceeding this in 5 of 8 patients with subacute pancreatitis, in 6 of the 12 patients with chronic relapsing pancreatitis, in none of the patients with pancreatic steatorrhea and in 4 of the 6 with pancreatic carcinoma. The increased urinary output of amylase usually was found in the first or second 2-hour specimen after stimulation.

Urine amylase output in control subjects increased by 0-81 units per hour after secretin stimulation. Increases ranging from 175 to 2,402 were found in 5 of 8 patients with pancreatitis, from 110 to 2,659 in 9 of 12 patients with chronic relapsing pancreatitis, from 0 to 80 in those with pancreatic steatorrhea and from 182 to 877 in 5 of 6 with pancreatic carcinoma. In only 6 of the 31 patients were substantial elevations in serum amylase levels found after secretin stimulation.

Radical Pancreatoduodenectomy: A 22-Year Experience with Complications, Mortality Rate and Survival Rate is

reported by James J. Mongé, Edward S. Judd and Robert P Gage.[8] A series of 239 cases consisting of 119 cases of cancer of the pancreas, 77 of carcinoma of the papilla of Vater, 25 of cancer of the duodenum and 18 of carcinoma of the common bile duct were treated surgically at the Mayo Clinic during 1941-62. Males predominated for each tumor site. The initial symptom was present an average of 9.3 months for patients with cancer of the pancreas, 8.5 months for those with cancer of the papilla of Vater, 16.8 months for those with cancer of the duodenum and 6.2 months for those with cancer of the common bile duct. The gallbladder was found to be distended in 127 of the 135 icteric patients.

Tumors of the region around the papilla of Vater were resected if there was no evidence of metastases or local invasion. Hemipancreatectomy was performed in 71 cases and total pancreatectomy in 12. An end-to-end pancreaticojejunostomy was constructed in 169 cases, an end-to-side anastomosis in 21, an end-to-end pancreaticoduodenostomy in 17 and pancreaticogastrostomy in 1. Choledochoenterostomy was performed for 224 cases, most often by an end-to-side technic. Most patients had the distal stomach removed and a retrocolic gastrojejunostomy constructed.

The resection rate was 72% for carcinoma of the papilla of Vater but only 10% for cancer of the head of the pancreas. The rates were intermediate in the other two categories of cancers.

The over-all hospital mortality was 19.2%: 21% for cancer of the head of the pancreas, 15.6% for cancer of the papilla, 24% for cancer of the duodenum and 16.7% for common duct carcinoma. Significant postoperative complications occurred in 156 patients, wound infection and pancreatic fistula appearing in 21 cases and gastrointestinal hemorrhage occurring in 20. Six patients had severe renal insufficiency, which accounted for 5 deaths. Of the 193 patients who survived operation, 75 had clinical steatorrhea and 29 had hyperglycemia usually requiring insulin therapy. Benign stenosis of the biliary-intestinal anastomosis occurred in 10 patients, 11 had dumping symptoms, and 3 had obstruction at the gastrojejunostomy; gastrojejunal ulcers developed in 3.

Survival rates are shown in the table. If 4 patients with islet cell carcinoma are excluded, the 5-year survival rate for

(8) Ann Surg 160 711 722, October, 1964

SURVIVAL RATES AFTER RADICAL PANCREATICODUODENECTOMY ACCORDING TO LOCATION OF MALIGNANT LESION

Location	Patients		Lived 3 or More Years After Operation		Patients		Lived 5 or More Years After Operation	
	Total	No Traced	No.	%	Total	No. Traced	No	%*
Head of pancreas	79	78	19	24 4	68	66	12	18.2
Papilla of Vater	55	53	29	54 7	48	46	18	39 1
Duodenum	16	16	7	43.8	13	13	5	38 5
Common duct	11	10	2	20 0	9	9	1	11 1
Totals	161	157	57	36 3	138	134	36	26 9

*Based on traced patients Inquiry as of Jan 1, 1964 Included in the 3-year group are patients operated on in 1960 or earlier, the 5-year group includes patients operated on in 1958 or earlier Hospital deaths are excluded in calculation of survival rates

ordinary ductal carcinoma of the pancreas was 14.3%. Factors influencing this survival rate were the pathologic type of cancer and its degree of local invasion. Even those who did not survive for a long time frequently benefited, with comfortable living secured as a result of the palliative procedure for periods of months to years.

► [In terms of survival of a number of patients admitted to the Mayo Clinic, 8 of 119 cases of cancer of the head of the pancreas proved operable and survived 5 years or more. This still is not an impressive figure, but even a 5% chance seems good compared to the figure of 0 so often quoted.—Ed.]