The British Society of Gastroenterology

The spring meeting was held at the University of Nottingham on 29 and 30 March 1974. The first morning was devoted to informal discussion groups, one of which was on ‘Histopathology of the alimentary tract’ (Chairman: Professor Ian Dawson) and the other on ‘Primary liver cancer’ (Chairman: Professor Sheila Sherlock). The whole of Saturday morning, 30 March, was devoted to a symposium on ‘Colonic function’. During the afternoon of both days there were sessions devoted to free papers of which abstracts follow.

Death after Partial Gastrectomy for Peptic Ulcer—A Long-term Study

N. A. DIN and W. P. SMALL (Gastro-Intestinal Unit and the Gastric Follow-up Clinic, Western General Hospital, Edinburgh)

After surgery for peptic ulcer, long-term survival is decreased. Krause (1958) showed this to be due to pulmonary tuberculosis, carcinoma of the stomach remnant, and suicide.

Westlund (1963) showed the ratio of actual to expected deaths to be 1:55:1 in males and 1:15:1 in females.

Follow-up of 400 patients over 15 years and of 1279 patients up to 25 years who underwent surgery for peptic ulcer at the Western General Hospital, Edinburgh, confirms an increased mortality in males, the ratio being 1:4:1.

The main causes of this increase have changed. Carcinoma of bronchus and ischaemic heart disease have replaced tuberculosis and carcinoma of the stomach. The majority of deaths occur six to 10 years after surgery.

This increased mortality is attributable not to the operation but to the effects of tobacco and alcohol. While the same pattern is developing in the general population, the trend is more advanced in the peptic ulcer group and particularly in patients submitted to surgery who have the largest share of bad habits.

There is a need for social re-education in this identifiable high-risk group to reduce the mortality from these preventable diseases. Such a move would make the ever-increasing refinements of surgical technique for treatment of peptic ulcer more meaningful.

References


Hospital Admission for Peptic Ulcer and Acute Gastrointestinal Bleeding in the United Kingdom 1958-70

R. C. BROWN and M. J. S. LANGMAN (Department of Medicine and Therapeutics, University of Nottingham)

Unpublished figures collected during the Hospital Inpatient Enquiry which examines a 10% sample of hospital discharges and deaths have been analysed to determine the pattern for gastric and duodenal ulcer and for haematemesis and melaena between 1958 and 1970.

During the period 1958 to 1961 approximately 33,000 patients with duodenal ulcer and 24,000 with gastric ulcer were admitted annually. Though duodenal ulcer admissions had only fallen very slightly by 1970, gastric ulcer admissions fell in the same period by a third. Analysis of the distribution of admissions by hospital regions showed a fairly even distribution for gastric ulcer, but a consistent tendency for duodenal ulcer to be more frequent in the north with especially high rates being recorded in Scotland.

By contrast to static or falling overall chronic ulcer admission rates, the frequency of admission with haematemesis or melaena of uncertain cause has risen by a third during the period under review. The cause of this trend, which is particularly obvious in younger men, is uncertain but it does not parallel national aspirin consumption figures which seem to be falling.

The Effects of Aspirin, Carbenoxolone, and Gefarnate on the Gastric Mucosal Potential Difference in Man

A. HOSSENBUCUS and D. G. COLLIN-JONES (Faculty of Medicine, Southampton General Hospital)

Carbenoxolone, and to a lesser extent gefarnate, have been shown to be effective in the treatment of gastric ulcers. Their ability to protect the gastric mucosa was assessed in patients with gastric ulcer or gastritis by measuring gastric potential difference (pd) and depression of pd (εpd) caused by 600 mg of aspirin (ASA) before and two to four weeks after starting treatment. Eighteen patients were treated with carbenoxolone and 11 with gefarnate.

There was no change in pd or εpd after treatment with gefarnate. Carbenoxolone produced no change in pd: −35.6 ± 2.3 mV before and −35.9 ± 2.6 mV (mean ± SE) after treatment. However, it produced a significant (p < 0.001) decrease in εpd: −52.4 ± 3.2% before and 37.3 ± 3.7% (mean ± SE) after treatment.

The pH of gastric contents was monitored with an intrastrach electrode in nine of the patients, before and after treatment with carbenoxolone. No significant change was observed.

Plasma salicylate levels were measured at intervals during the tests. There was no difference between the levels attained in the carbenoxolone-treated and the untreated groups. When εpd was plotted against plasma salicylate levels, two parallel regression lines were obtained, εpd being 14.7% lower for those treated with carbenoxolone than for untreated patients at any salicylate level (p < 0.001).

These findings support the hypothesis that carbenoxolone protects the gastric mucosa against damage by aspirin. This protection does not depend upon any change in pH or in ability to absorb aspirin. Gefarnate, on the other hand, could not be shown to exert the same protective effect.

References


The pH-Dependent Effect of Sodium Taurocholate on Increasing Gastric Mucosal Permeability

DESMOND BIRKETT AND WILLIAM SILLEN (sponsored by PROFESSOR IAN MCCOLL) (Departments of Surgery, Harvard Medical School and Beth Israel Hospital, Boston, Massachusetts, and Guy’s Hospital, London) Bile salts increase the gastric mucosal permeability, but the influence of pH on their action is uncertain. Black has shown a marked pH-dependent effect, whereas Davenport showed none. To investigate this further we studied the effect of sodium taurocholate (Tch) on the permeability in vitro of rabbit fundic gastric mucosa at differing pH values by measuring the mucosal to serosal flux of erythritol-C14. At pH 7.0 the mucosal flux of erythritol in normal mucosa was 1.85 ± 0.25 picomoles/cm2/sec, and 10 and 20 mM Tch increased the rate to 1.93 ± 0.34 and 5.46 ± 0.54 picomoles/cm2/sec respectively after one hour, and 3.18 ± 0.53 and 10.10 ± 1.20 picomoles/cm2/sec respectively after two hours. At pH 3.0 the effect was greater. The flux rates of 2.5, 5.0, and 10 mM Tch were 3.98 ± 1.29, 5.81 ± 1.37, and 13.52 ± 2.31 picomoles/cm2/sec respectively after one hour, and 5.69 ± 1.34, 7.77 ± 1.54, and 23.87 ± 4.97 picomoles/cm2/sec respectively after two hours: 20 mM Tch at pH 7.0 and 5 mM Tch at pH 3.0 increased the permeability to a similar degree; this is a fourfold reduction in dose for a moderate reduction of pH. At these pH values Tch is in the ionized, lipid-insoluble form as they are above its pKa, and therefore it penetrates the mucosa to a small extent. This marked pH-dependent effect of sodium taurocholate on gastric mucosal permeability must be due to an effect of back diffusion of hydrogen ions superimposed on the effect of sodium taurocholate.

References

Postoperative Duodenogastric Reflux: A Cause of Gastritis and Symptoms

M. R. B. KEIGHLEY, P. ASQUITH, AND J. ALEXANDER-WILLIAMS (University Department of Surgery, The General Hospital, Birmingham) Many patients who have continued dyspepsia but no recurrent ulcer after gastric surgery have endoscopic evidence of gastritis associated with the presence of bile in the stomach. In these subjects the results of further gastric surgery are particularly disappointing (Halpern, Hirschowitz, and Moody, 1973) and it has been suggested that one of the reasons for failure is that their symptoms are associated with duodenal reflux. To investigate this hypothesis we studied 30 patients one to seven years after 'ulcer curative' operations (truncal vagotomy and pyloroplasty 14; Billroth I gastrectomy 6; proximal gastric vagotomy 4; others 6). Twelve had no symptoms, 18 had dyspepsia, including 11 with symptoms suggesting reflux. Biliary disease and hiatus hernia were excluded in all subjects. Assessment was by a seven-point symptomatic score, measurement of bilirubin and sodium concentrations from 10-minute samples of resting gastric juice, endoscopy, and biopsy. In addition fluoroscopic demonstration of reflux was assessed using a modification of the technique described by Capper (1966). Of 11 patients with severe symptoms, radiological reflux and severe gastritis occurred in six, and heavy bile contamination of resting juice in five. In the 12 asymptomatic patients there was no radiographic or biochemical evidence of reflux and the presence of gastritis was found in only one. There is a significant correlation between the presence of gastritis, dyspeptic symptoms, and duodenal reflux (p < 0.01).

References

Gastric Epithelial Cell Turnover after Acute and Chronic Alcoholic Ingestion

N. KRAISNEL, T. J. THOMSON, G. CREAN, AND C. MCNEIL (Gastrointestinal Units, Stobhill General Hospital and Southern General Hospital, Glasgow) The purpose of this study was to investigate the effect of excessive alcohol consumption on the rate of turnover of epithelial cells in the stomach (CTR). The method of Croft, Pollock, and Coghill (1966) estimating deoxyribonucleic acid in gastric washings was used.

Cell turnover rate was measured in 21 chronic alcoholic patients, seven patients who had consumed an acute excess of alcohol, and eight healthy volunteers who acted as a control group. The results expressed as nanograms of DNA-P per minute were as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>CTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic alcoholics (all)</td>
<td>19.4 ± 13.3</td>
</tr>
<tr>
<td>Alcoholics without ulcers</td>
<td>18.4 ± 12.9</td>
</tr>
<tr>
<td>Acute effects of alcohol</td>
<td>31.3 ± 12.1</td>
</tr>
<tr>
<td>Controls</td>
<td>13.1 ± 4.9</td>
</tr>
</tbody>
</table>

Cell turnover rates were significantly greater after acute exposure to alcohol than in both the control group (p < 0.005) and the chronic alcoholic group (p < 0.05). Of the 21 chronic alcoholics, eight had radiological evidence of peptic ulceration, five having duodenal ulcers and three with gastric ulcers. There was no significant difference between the chronic alcoholic group with and without ulcers.

It is concluded that following acute exposure to alcohol the gastric epithelial CTR is markedly elevated while chronic alcoholism does not significantly alter cell turnover rate.

Reference

A Morphological and Pharmacological Study of the Parietal Cells of the Stomach in the Dog during Periods of Maximal Acid Output and after the Gastric Secretory Inhibitor UK-9040

D. B. HAMER, A. B. PRICE, AND J. H. BARON (Department of Surgery, Royal Postgraduate Medical School, and Department of Pathology, St Mark's Hospital, London) The search for effective medical treatment of peptic ulceration has led to the development of UK-9040 (cis-1-(5-neopentyl-2-thienyl)-1-phenyl-4-pyrrolidinobut-1-ene), a powerful inhibitor of gastric acid secretion and an analogue of the conventional antihistamines.

Four dogs with gastric fistulae and Heidenhain pouches were given varying quantities of oral UK-9040. This produced almost complete inhibition of pepsin and titratable acidity after doses of pentagastrin, insulin, histamine, and a
standard meal. In the course of these experiments biopsies for light and electron microscopy were taken from the lesser curve of the stomach with a Wood's tube. No changes were seen with the light microscope. Electron micrographs confirmed the appearances seen in normal resting and actively secreting parietal cells. However, the characteristic secretory change of tubulovesicular depletion was inhibited in the majority of cells after the administration of UK-9040.

Prolonged administration of the drug to one dog did not produce tolerance, acid secretion remaining inhibited. Biopsies from this animal when compared with those from the short-term experiments were similar. In all animals withdrawing the drug resulted in a return to a normal physiological and morphological response.

This drug arrests the functional and morphological secretion of canine parietal cells.

Effect of H₂-Receptor Blockade on Vagally Induced Gastric Secretion and Gastric Emptying in Man

D. C. CARTER, M. WERNER, J. A. H. FORREST, R. C. HEADING, J. PARK, and D. J. C. SHEARMAN (Departments of Clinical Surgery and the Gastrointestinal Section of the University Department of Therapeutics, Royal Infirmary, Edinburgh) Conventional antihistamines do not block the stimulation of gastric secretion. The new H₂-receptor blocking drug, metiamide, inhibits histamine- and pentagastrin-induced secretion in man (Wyllie, Ealding, Hesselbo and Black, 1973) but its effects on vagally induced secretion and the rate of gastric emptying are unknown.

Vagal stimulation was achieved by continuous insulin infusion (0.03 units/kg/hour) (Carter, Dozois, and Kirkpatrick, 1972) in six healthy male volunteers. The volume and acid concentration were reduced by simultaneous iv infusion of 200 mg metiamide/hour. The mean pLAI of 6.22 ± SD 3.7 mmol/hour was significantly lower than in paired control tests (20.9 ± SD 6.4 mmol/hour; \( p < 0.001 \)). Paired tests were also performed in four peptic ulcer patients, using 0.04 units insulin/kg/hour as a vagal stimulus. The mean pLAI during simultaneous metiamide infusion (9.3 ± SD 8.1 mmol/hour) was again significantly lower than in control tests (29.1 ± SD 13.0 mmol/hour; \( p < 0.01 \)). The effect of metiamide on gastric emptying was determined by paired measurements of emptying rate using a scintiscanning method (Heading, Tothill, Laidlaw, and Shearmar, 1971). Oral administration of 400 mg metiamide 20 minutes before the study retarded emptying in 12 of 14 peptic ulcer patients. Metiamide is thus a potent inhibitor of vagally induced gastric secretion and there is preliminary evidence that it also delays gastric emptying.

Inhibition of Nocturnal Acid Secretion in Duodenal Ulcer by Oral Metiamide

J. G. WILLIAMS and G. J. MILTON-THOMPSON
(Royal Naval Hospital, Plymouth) and D. J. A. JENKINS and J. J. MISIEWICZ (MRC Gastroenterology Unit, Central Middlesex Hospital, London) Metiamide is a histamine H₂ receptor antagonist (Black, Duncan, Durant, Galanlin, and Parsons, 1972), shown to be an effective inhibitor of gastric acid secretion in normals (Wyllie and Hesselbo, 1973). Nocturnal pain is a frequent symptom in duodenal ulceration and overnight secretion of acid in this disease is often high. We have studied the effect of a single oral dose of 400 mg of metiamide on the overnight acid secretion in 11 patients with duodenal ulcer. Each was studied on two occasions, receiving either the drug or placebo according to a predetermined random order. After a one-hr baseline period, the tablets were swallowed with 250 ml of water and the collection of juice was discontinued for one hour. The stomach was then emptied: measurements of residual metiamide showed that 80-100% of the dose had left the stomach. Gastric secretion was collected continuously for a further six hr and half-hourly samples were analysed in the usual way. Plasma gastrin was measured before and after the drug.

Ten of the 11 patients responded to metiamide. There was a striking and highly significant reduction of acid output and rise in pH (\( p < 0.01 \) to \( 0.05 \)), which persisted for six hours after the drug. In five patients the pH remained above 5 for five hr after the drug. Eight patients were acidemic for periods ranging from one to seven hours. Plasma gastrin levels were unchanged. There were no side effects.

These results indicate that metiamide may be useful in the treatment of nocturnal symptoms of duodenal ulcer.

References


Initial Observations on the Inhibitory Action of Urogastrone on Gastric Secretory Responses in Man

I. E. GILLESPIE, J. B. ELDER, P. C. GANGULI, H. GREGORY, and L. GERRING (University Department of Surgery, Manchester Royal Infirmary, and ICI Ltd, Alderley Edge, Cheshire) Although the existence of a powerful inhibitor of gastric secretion in urine has been known for many years, only recently has there been available a small quantity of extract of sufficient purity for administration to humans.

The effects of one-hour iv infusions of 0.125, 0.25, and 0.5 mg/kg on the acid responses to continuous iv infusions of pentagastrin, 0.2 µg/kg/hour, histamine acid phosphate 10 µg/kg/hour, and single subcutaneous injections of soluble insulin, 0.2 units/kg, were observed in 12 normal healthy male volunteers. All three doses of urogastrone inhibited the acid responses to pentagastrin in all subjects, the mean reduction in output being 60%, 85%, and 90% respectively for the 0.125, 0.25, and 0.5 mg/kg/hour doses of urogastrone. Less marked inhibition was noted in the secretion of intrinsic factor and of pepsin. Serum gastrin concentrations were not affected.

The inhibitor effect of urogastrone was less on the secretory responses to histamine and to insulin.

Throughout each experimental run repeated measurements were made of pulse, blood pressure, and temperature, and blood was taken before, during, and at 24 and 36 hours after the infusions for estimations of Hb, WBC, film, platelets, urea, and electrolyte concentrations and liver function test. Apart from transient headache in two subjects with only the largest dose of urogastrone, there were no side effects or alterations in any haematological or biochemical measurement.
Secretin Release in Man after Intraduodenal Acid

S. R. Bloom and A. S. Ward (c/o M. Hobsley, Middlesex Hospital, London)

A sensitive radioimmunoassay for plasma secretin has been set up with antibodies raised to natural and synthetic secretin. Synthetic tyrosinic secretin (1 or 6 position) or natural secretin iode 125 was used as tracer. Changes of 25 pg/ml plasma can be detected with 95% confidence and fasting levels have been found to be below 50 pg/ml.

Secretin release was studied by intraduodenal infusions of 40 ml of 0.1 N HCl over five minutes. In five normal volunteers plasma secretin peaked at six minutes, with a mean rise of 46 pg/ml (SE 8.3), and returned to baseline by 15 minutes. In 11 patients with duodenal ulceration secretin rose by only 21 pg/ml (SE 6.4) at six minutes and returned to baseline by 10 minutes. The duodenal acid infusion produced an inhibition of pentagastrin-stimulated gastric secretion. Four subjects, who received an exogenous secretin infusion at a dose known to produce a small inhibition of pentagastrin-stimulated gastric secretion (0.5 U/kg over eight minutes) had a mean peak plasma increment of 1045 pg/ml (SE 125).

Thus there appears to be impaired secretin release in patients with duodenal ulceration and there is a discrepancy between the endogenous and exogenous secretin levels normally produced in gastric acid inhibition studies.

Abnormalities of Cholecystokinin Secretion and Gallbladder Emptying in Coeliac Disease

T. S. Low-Beer, R. F. Harvey, D. Nolan, E. R. Davies, and A. E. Read (University Departments of Medicine and Radiology, Bristol Royal Infirmary, Bristol) In order to investigate the abnormality of gallbladder function in coeliac disease (CD) (Low-Beer, Heaton, Heaton, and Read, 1971), we have measured gallbladder emptying by a radioisotopic technique (Englert and Child, 1966; Low-Beer, Nolan, and Davies, 1974), and related it to serum cholecystokinin (CCK) levels measured by radioimmunoassay (Harvey, Dowsett, Hartog, and Read, 1973) in 10 patients with untreated CD and 10 control subjects after a standard fatty 'meal' containing 20 ml arachis oil.

Fasting serum CCK was markedly raised in patients with CD (mean 1082 pg/ml) compared with normals (mean 68 pg/ml, p < 0.0025), but the rise of serum CCK after the meal was slower than in control subjects, so that by 30 minutes the mean levels in the two groups were similar, and peak levels were not significantly different (CD: mean 4274 pg/ml, controls: 4940 pg/ml, p < 0.050). Gallbladder emptying, which began within 12 minutes after the meal in all of the control subjects (mean 9.2 minutes), was significantly delayed in patients with CD (mean 24.6 minutes, p < 0.0025), who appeared to require a greater increment of serum CCK for gallbladder contraction to begin. We conclude that at least two factors contribute to the defective gallbladder emptying in patients with coeliac disease. First the rise in serum CCK is less steep than normal. Secondly the gallbladder appears to be less sensitive to the action of CCK, possibly as a result of the abnormally high fasting levels.

References


Collagenous Basement Membrane Thickening in Jejunal Biopsies from Patients with Adult Coeliac Disease

R. Bossart, K. Henry, William F. Doe, and C. C. Booth (Departments of Medicine and Histopathology, Royal Postgraduate Medical School, London) Collagenous basement membrane thickening is observed in a significant proportion of jejunal biopsies from patients with adult coeliac disease (Hourihane, 1963). In 1970 Weinstein, Saunders, Tytgat, and Rubin described a condition characterized by malabsorption, a flat jejunal mucosa with a dense deposit of collagen beneath the basement membrane, and failure to respond to a gluten-free diet. They named this condition 'collagenous sprue'. To address the relationship between these two conditions, histological sections of 145 jejunal biopsies from 145 patients with adult coeliac disease were examined for the presence of basement membrane thickening and collagen deposition. Jejunal biopsies from patients suffering from other small intestinal disorders served as controls.

Biopsies from 45 (31%) coeliac patients showed basement membrane thickening often associated with deposition of collagen beneath the basement membrane. In 11 patients these collagen deposits were dense and in the other 34 patients basement membrane thickening was the predominant finding. No basement membrane thickening or collagen deposits were seen in control biopsies. Fatal, unremitting malabsorption developed in four coeliac patients whose jejunal biopsies showed dense collagen deposition beneath the basement membrane.

These findings confirm that collagenous membrane thickening is a frequent finding in jejunal biopsies from patients with adult coeliac disease. The presence of dense collagen deposits beneath the basement membrane, however, may indicate a poor prognosis.

References


The Cellular Infiltrate of the Jejunum in Coeliac Patients with Complicating Lymphoma

R. Ferguson, P. Asquith, and W. T. Cooke (The Nutritional and Intestinal Unit, General Hospital, Birmingham, and the Department of Experimental Pathology, University of Birmingham) Although there is an increased incidence of lymphoma in adult coeliac disease, the cause remains obscure. Decreased immunological surveillance has been suggested as a possible mechanism and in support of such a hypothesis lymphocytes from coeliac patients show impaired PHA transformation and altered responses to EB2 cells.

Reports quantitating cells in jejunal biopsies from patients with uncomplicated coeliac disease have shown a marked increase in plasma cells and a decrease in lymphocytes in the lamina propria and an increase in intraepithelial lymphocytes (Holmes, Asquith, Stokes, and Cooke, 1973). To test whether this also applied...
to patients developing lymphoma, biopsies from 18 such patients were studied; in six patients two or more serial biopsies were available. Results were compared with 15 healthy controls and 30 other coeliacs of whom 15 were on a gluten-free diet. Results in uncomplicated coeliac disease confirmed previous studies but in lymphoma patients, although the cell counts were abnormal, they were significantly different from other coeliacs. Changes also tended to be present up to several years before the lymphoma was diagnosed. The results suggest that the immunological status of these patients differs from other coeliacs, that it could represent a primary abnormality and could be relevant to the aetiology and diagnosis of lymphoma.

References


Immunological Phenomena following Gluten Challenge in the Jejunum of Patients with Adult Coeliac Disease and Dermatitis Herpetiformis

M. LANCASTER-SMITH, PARVEEN KUMAR, AND M. L. CLARK (Department of Gastroenterology, St Bartholomew’s Hospital, London) The cellular infiltrate of the lamina propria is an important feature of the jejunal lesion in gluten-sensitive enteropathy. We have studied the effect of gluten on the jejunal mucosa, using histological and immunofluorescent techniques in 10 patients with adult coeliac disease (ACD) and in seven with dermatitis herpetiformis (DH); all patients were on a gluten-free diet and had no abnormality or mild partial villous atrophy of the jejunum. Serial biopsies before and after either a single challenge of 25 g of gluten or taking a gluten-containing diet for seven days were studied.

Comparable changes were found in both ACD and DH. Total cell counts were increased at 24 hours and within 48 hours there was a rise in both IgA- and IgM-containing cells. However, despite this increase, IgA cell numbers remained within the normal range even after seven days on a gluten-containing diet. This contrasted with IgM cells which in all but one case rose to levels well above normal. Small numbers of eosinophils and neutrophils were seen but no immunoglobulin or complement-containing aggregates were demonstrated as previously described in childhood coeliac disease (Shiner and Ballard, 1972). These findings suggest that the same humoral mechanisms are important in the pathogenesis of the jejunal lesion in both ACD and DH and that both IgA and IgM systems are involved.

Reference


Coeliac Disease, Malignancy, and Gluten-free Diet

G. K. T. HOLMES, P. L. STOKES, R. MCWALTER, J. A. H. WATERHOUSE, AND W. T. COOKE (The Nutritional and Intestinal Unit, The General Hospital, Birmingham) An analysis of 208 coeliac patients, all with characteristic jejunal biopsies studied between 1939 and 1972, has been made of the incidence of malignancy and of the effect of a gluten-free diet in modifying this. The number of cancer deaths was compared with those expected based upon the rates prevailing in the local population and calculated using the method of years at risk with a midpoint mortality rate for the series taken from the Case-Pearson tables. Statistically significant increases of all cancers, carcinoma of the oesophagus, and reticulosarcomas were found. The duration of symptoms of coeliac disease before those attributed to reticulosarcoma averaged 22 years and for carcinoma 31 years. When men and women were considered together those on a normal diet were subject to increased risks of cancer at all sites (p < 0.001) but those treated with a gluten-free diet for at least 12 months irrespective of their clinical response were not at greater risk than the population as a whole. In contrast, the incidence of reticulo-sarcoma though less in those on a gluten-free diet was significantly greater in both groups (p < 0.001).

A Study of the Electrical Potential Difference (PD) across Human Ileostomy Mucosa

P. ISAACS AND L. A. TURNBERG (Manchester Royal Infirmary and Hope Hospital, Salford) Potential difference was measured across ileal mucosa in patients with ileostomies using a KCl/agar probe and a reference electrode attached to the skin. In 18 clinically fit subjects the mean pd was 16 mV ± 1·48 (1 SEM), lumen negative. It was lower during the first two weeks after operation (10·86 mV ± 1·49) but thereafter varied little over 18 months and did not vary when measured repeatedly over a single 24-hour period. The pd at 7 to 10 cm deep to the stoma was lower than at 2 to 5 cm (mean 7·8 mV compared with 16 mV) but both these are higher than has been reported in the normal terminal ileum (Sachar et al, 1969; Turnberg et al, 1970).

Patients judged clinically and on the basis of serum and urine electrolytes to be dehydrated and sodium depleted had pd values similar to those in fit patients. There was no correlation between the Na+/K+ ratio in urine and ileostomy ejeecta or between these ratios and pd. These findings suggest that salt-retaining steroids were exerting little influence on ileal ion transport.

This simple and reliable technique can provide useful information about ileal function and here the pd was used to predict the possibility that the high mean K+ in ileostomy ejeecta (9·06 m-equiv/l, range 5·2 to 20·3) was due to active K+ secretion.

References


Functional Differentiation of the Human Jejunum and Ileum

D. B. A. SILK, JOAN P. W. WEBB, ANETTE E. LANE, M. L. CLARK, AND A. M. DAWSON (Departments of Medicine and Gastroenterology, St Bartholomew’s Hospital, London) Animal experiments have demonstrated a decreased efficiency of absorption of sugars and some amino acids in the ileum compared with the jejunum. In order to investigate the magnitude of this gradient in man, a perfusion technique has been used (Sladen and Dawson, 1970). Jejunal and ileal absorption of glucose, glycine, and L-alanine as well as glycyl-L-alanine have been studied in six normal subjects. The correct siting of the perfusion tube in the ileum was confirmed by studying bicarbonate absorption, for Phillips and Summerskill (1967) showed that whereas this ion was absorbed in the human jejunum, secretion occurred in the ileum.

There was a 45·1% reduction in the mean glucose absorption rate, a 55·5% reduction in the mean glycine absorption
rate, and a 17.9% reduction in the mean L-alanine absorption rate between the jejunum and ileum. In contrast, the dipeptide glycyl-L-alanine was absorbed at comparable rates from the two sites.

The results lend further support for the existence of separate mechanisms for amino acid and dipeptide transport in man because there was an absorptive gradient for the free amino acids between the jejunum and ileum which was not apparent when the dipeptide was perfused. Higher concentrations of free glycine (p < 0.02) and free L-alanine (p < 0.01) were aspirated during the ileal compared with the jejunal dipeptide perfusions. These differences are likely to be due to the differential in absorption rates of the free amino acids in the jejunum and ileum, rather than to differences in mucosal peptidase activity because glycyl-L-alanine was hydrolysed at comparable rates in vitro by jejunal and ileal intraluminal peptidases.

References

The Effects of Different Doses of Cheno-
deoxygenic Acid and of Withdrawing
Treatment on Bile Lipid Composition and
Liver Function in Patients with Gallstones
H. Y. I. Mok, G. D. Bell, and R. Hermon Dowling (Departments of Medicine, Royal Postgraduate and Guy's Hospital Medical Schools, London) Although relatively large doses of chenodeoxygenic acid (CDCA) dissolve gallstones, recent animal studies suggest that it may be hepatotoxic. Since previous doses of CDCA were chosen empirically and the effect of withdrawing therapy is unknown, we studied bile lipid composition and liver function in patients with gallstones after smaller doses of CDCA and examined cholesterol saturation of bile after cessation of treatment.

The biliary cholesterol solubilizing capacity was increased from 11.6 ± 3.3 to 17.0 ± 1.7 on 250 mg CDCA/day; from 12.3 ± 1.0 to 19.0 ± 2.3 on 500 mg; 12.7 ± 1.1 to 19.7 ± 2.8 on 750 mg and from 12.1 ± 0.5 to 20.6 ± 1.2 on 1000 mg/day, and correlated significantly with dose per kg body weight. Similar results were found when different doses were given to the same individuals. Transient elevations of serum hepatocellular enzymes (ICD and SCOT) were found in six of 31 patients on 750-1000 mg CDCA/day but in only one of 21 patients on lower doses. These enzymes returned to normal either spontaneously or on reducing CDCA dosage. Cholesterol solubility in bile deteriorated in six of eight patients (17.3 ± 1.5 to 10.1 ± 1.0) three months after withdrawing CDCA.

In conclusion, both cholesterol solubility and the incidence of raised hepatocellular enzymes are related to dose of CDCA: once gallstones have dissolved, long-term maintenance therapy may be necessary.

A Malabsorption Syndrome in Overland Travellers to India: Mucosal Colonization by Bacteria
A. M. Tomkins, W. P. T. James, and B. S. Drasar (Clinical Nutrition and Metabolism Unit, London School of Hygiene and Tropical Medicine, and Bacterial Metabolism Research Laboratory, Colindale) A new group of patients with tropical malabsorption is described. Typically young adults, they develop diarrhoea during an overland journey to the Indian subcontinent. Thirty-four patients, without parasitic infestation, with diarrhoea of one to nine months' duration, were investigated. Mean 24-hour stool weights on a standard 97-105 g fat diet were 394 ± 57 SEM (range 180-1421 g). Twenty-nine of 31 patients on the diet had statorrhoea; all except one had xylose malabsorption and 11 of 12 had B12 malabsorption. Jejunal morphology was always abnormal with a more severe lesion in those with protracted diarrhoea; decreasing folate levels related to duration of symptoms. 14C glycocholate breath tests were negative in 11 of 11 patients.

Simultaneous samples of jejunal mucosa and luminal fluid were cultured for aerobic bacteria in nine patients. All nine had significant contamination of the mucosa itself with 10^3-10^8 bacteria per g. Luminal fluid tended to have fewer bacteria but still > 10^4 organisms/mL. Successful treatment led to an elimination of mucosal bacteria and histological improvement. Mucosal colonization by bacteria appears to be of significance in maintaining the mucosal lesion of tropical sprue.

Plasma Levels of Amino Acids and Gluca-
gon in Patients with Pancreatic Gluca-
gonomas
C. N. Mallinson, B. Cox, and S. R. Bloom (Greenwich Hospital G.I. Unit, Department of Medicine, Guy's Hospital Medical School, London) At the last meeting of the Society we described a syndrome of dermatosis, diabetes, anaemia, and weight loss associated with pancreatic islet-cell tumours containing glucagon and high plasma glucagon levels (Mallinson, Salmon, Barrowman, and Bloom, 1973). It was suggested that the effect of the glucagon on amino acid metabolism could account for the clinical features. Plasma glucagon (pg) has been measured by radioimmunoassay and plasma amino acids (paa) by ion-exchange chromatography in four patients with the above clinical features and high plasma glucagon levels, in three of whom a pancreatic glucagonoma had been found. In exacerbations of the syndrome all four patients showed very high pg and low paa levels. Arginine stimulation did not alter these values. Following surgical 'cure' of the syndrome both pg and paa promptly returned to normal. During clinical remission pg and paa were less grossly abnormal than in patients in exacerbation. Successful treatment of the rash with dideoxynucleotide resulted in return to normal values of paa. Pharmacological suppression for one hour of glucagon and insulin secretion lowered pg values markedly but had no effect on paa. These results are consistent with the hypothesis that amino acid metabolism is an intermediate in the pancreatic glucagon syndrome.

A Prospective Survey of the Treatment of Acute Pancreatitis
C. W. Imrie, A. S. Whyte, and L. H. Blumgart: A prospective study of 78 cases of acute pancreatitis documented over two years is presented. Regular follow up of 94% of patients has been achieved. Thirty-nine patients (50%) had unequivocal evidence of biliary disease. Alcohol-associated acute pancreatitis occurred in 20 cases (26%) of whom all

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but one were male. Two cases occurred in association with pancreatic carcinoma. No associated aetiological factor could be implicated in seven patients.

Neither Trasylol (aprotinin) nor glucagon were part of the management regime. The mortality for the 67 patients managed by conservative regime was 6%. However, in the remaining 11 cases early surgery was performed, usually on uncertainty of diagnosis, and five of this group died. Of the patients with proven biliary disease, 29 were submitted to elective biliary surgery and only one sustained a further major attack of pancreatitis this being related to a retained common bile duct stone.

The overall mortality for the series was 11.5%. The results of this study compare favourably with reports on the use of Trasylol (Tranell, Rigby, Talbot, and Duncan, 1973) and glucagon (Condon, Knight and Day, 1973) and underline the necessity for further carefully controlled clinical trials before accepting these agents as beneficial in the treatment of acute pancreatitis.

References


Serological Findings amongst Domestic Contacts of Persons with Transient and Persistent Hepatitis B Antigenemia

PH. GATEAU, JENNY HEATHCOTE, AND SHEILA SHERLOCK (Department of Medicine, Royal Free Hospital, London) Serum hepatitis B antibody (HB-Ab) has been sought, by the passive haemagglutination serum technique, amongst the domestic contacts of 39 hepatitis B antigen (HB-Ag)-positive subjects.

Monthly serum samples were obtained from 10 patients with acute type B hepatitis during their convalescence. Five had HB-Ab detected transiently. Six of their 23 contacts, similarly, had antibody detected, mostly commonly three months after the propositus suffered hepatitis. Three were blood relatives.

Fifty-nine household members of 29 persistently HB-Ag positive individuals were tested for both HB-Ag (by counter-immunoelectrophoresis) and HB-Ab. Twelve subjects were healthy carriers of the HB-Ag; only two of their 21 contacts had HB-Ab and none were HB-Ag positive.

Liver Disease in Healthy Blood Donors Associated with Presence of Hepatitis B Antibody

B. E. BOYES, L. L. WOOLF, J. S. WHITTAKER, E. TAPP, D. M. JONES, P. H. RENTON, F. STRATTON, R. MCSWEEN, AND I. W. DYMOCK (Departments of Medicine, Pathology and Bacteriology, University Hospital of South Manchester, The National Blood Transfusion Service, Manchester, and the University Department of Pathology, Western Infirmary, Glasgow) In a previous communication to this Society we reported on the occurrence of liver disease in asymptomatic blood donors who were carriers of the hepatitis B antigen (HB-Ag). In addition to this routine testing of donor blood for HB-Ag all donations have been screened for the hepatitis B antibody (HB-Ab). In the period from December 1970 95 donors who were HB-Ag positive and HB-Ab negative have been referred for clinical assessment at the Liver Clinic.

All 95 were asymptomatic. In each instance a careful history was taken to elicite a possible exposure to HB-Ag. Thirty of the donors had been in close contact with hepatitis patients but none had themselves been jaundiced. Twelve were tattooed, 12 had previously received blood transfusion, and nine were hospital staff members. None of the 95 had any stigmata of liver disease but 15 had abnormal routine liver function tests. Liver biopsies were obtained from 11 donors. Only three biopsies were normal, the remainder showing focal parenchymal necrosis in five and chronic persistent hepatitis in three.

It is concluded that the presence of HB-Ab may sometimes be associated with liver changes similar to those found in HB-Ag carriers.

Cell-mediated Immunity to Hepatitis B Antigen in Antigen-negative Active Chronic Hepatitis

W. D. REED, W. M. LEE, A. L. W. F. EDDLESTON, C. G. MITCHELL, A. J. ZUCKERMAN, AND ROGER WILLIAMS (The Liver Unit, King’s College Hospital, London, and London School of Hygiene and Tropical Medicine) Eighteen per cent of a series of 94 patients with active chronic hepatitis (ACH) were found to have hepatitis B antigen (HB-Ag) in the serum. However, apart from an increased frequency in males and those born overseas, no significant differences were found in clinical
manifestations, autoantibodies, and prognosis between antigen-positive and antigen-negative cases (Reed, Eddleston, Stern, Williams, Zuckerman, Bowes, and Earl, 1973). The latter group has now been examined further for evidence of previous infection with hepatitis B virus using the leucocyte migration test as a measure of cell-mediated immunity with a column purified preparation of HB-Ag as antigen.

Positive responses were detected in 24 (63%) of 38 patients with antigen-negative ACH which was significantly higher (p < 0.01) than the 30% found in 43 healthy controls. This finding suggests that infection with the hepatitis B virus may be of importance in the aetiology of the disease in antigen-negative as well as antigen-positive cases. Only three (27%) of the 11 patients in the antigen-positive group had evidence of cell-mediated immunity to HB-Ag and the lack, in most of these cases, of an appropriate immune response may underly their failure to eliminate the infecting virus.

When cell-mediated immune responses to a liver cell membrane antigen were measured, the frequency of positive reactions in the HB-Ag-negative and -positive cases (51 and 53% respectively) was similar. This lends further support to the proposal that a common autoimmune process is involved in the pathogenesis of the progressive liver cell damage in both groups of patients.

References

**67Ga Citrate Liver Scanning: Evaluation of its Use in 80 Patients and Evidence of Intrahepatic Distribution by Autoradiography**

OLIVER JAMES, J. WOOD, M. MAZE, L. C. GAYOTTO, H. S. WILLIAMS, AND SHEILA SHERLOCK (Departments of Medicine, Physics, and Pathology, Royal Free Hospital, London) The radionuclide **67Ga** has recently been shown to be taken up selectively in soft tissue tumours and inflammatory lesions throughout the body (Edwards and Hayes, 1969; Lomas Dibos, and Wagner, 1972).

In the present study **67Ga** liver scans have been carried out in 80 patients following **19mTc** colloid scan in order to evaluate the value of **67Ga** liver scanning in the diagnosis of liver disease.

The **67Ga** scan was found to be valuable in the diagnosis of primary liver cell carcinoma, particularly in the presence of cirrhosis. The scan was positive in 22 of 24 patients with biopsy proven primary liver cell cancer whereas no positive results were obtained in 20 scans carried out on patients with cirrhosis but no primary liver cell cancer. **67Ga** scanning was also found to be of value in the diagnosis of pyogenic abscess, particularly on the edge of the liver where colloid scan may give an equivocal result. Seven of seven **67Ga** scans were positive in this group. The results obtained in patients with bile duct carcinoma, secondary hepatic metastases, other intrahepatic lesions, and hepatitis are also presented.

The distribution of **67Ga** within the liver in different circumstances has been investigated by autoradiography. The findings will be discussed.

References

**The Progress of Children with Intrahepatic Cholestasis**

JENNY HEATHCOTE, K. P. DEODHAR, P. J. SCHEUER, AND S. SHERLOCK (Department of Medicine and Department of Pathology, Royal Free Hospital, London) Sixteen children with prolonged cholestasis have been observed. Fifteen presented with jaundice, 13 within one month of birth. Three presented later, one at 6 years, with pruritis. Nine were thought clinically to have hepatitis, in five liver histology supported this diagnosis and in two others serum rubella antibody in high titre was found. The initial diagnosis was uncertain in the remaining seven. Two of the 16 are siblings and the brother of another had 'neonatal hepatitis'. Four mothers took progesterone during pregnancy.

Cholestasis persisted in all 16; laparotomies were performed in 13 and in 11 operative cholangiography demonstrated a patent extrahepatic biliary system.

Two have died before 3 years. The 14 living are mentally normal and only four are stunted and ill. All but two have continual pruritis and 11 have persistent or fluctuant jaundice. Survivors have cholestatic liver function tests, but xanthomas are present in only three. In all 10 tested HB antigen is negative and mitochondrial antibodies are absent. Fifty per cent have hepatosplenomegaly. Liver biopsies show a variety of lesions including cirrhosis, but there is no consistent abnormality of small bile ducts.

Twelve patients have now reached their fifth year and four are over 18 years old.

**Biocompatibility in a System of Artificial Liver Support for Fulminant Hepatic Failure**

M. J. WESTON, B. G. GAZZARD, P. G. LANGLEY, E. H. DUNLOP, AND ROGER WILLIAMS (From the Liver Unit, King's College Hospital and Medical School, London) Haemoperfusion through activated charcoal and ion-exchange resins for the removal of water-soluble and protein-bound metabolites respectively is a possible basis for an artificial liver support system. Unfortunately, platelets and white cells are also adsorbed. Studies in vitro showed that coating the charcoal with the polymer 'polyhema' reduced the platelet adherence but the thickness of this coating and the method of application are of critical importance in determining both biocompatibility and the rate of removal of metabolites. A 4% by weight coating applied by an encapsulation technique appeared to be the most suitable for clinical use.

Haemoperfusion through charcoal with a 4% w/w polyhema coating in the dog reduced the platelet count by only 20% over a four-hour period. The biocompatibility of the coating was also satisfactory in other respects. No haemolysis or changes in electrolytes and clotting factors were detected.

So far 42 treatments have been carried out using a charcoal perfusion column in 13 patients whose condition had deteriorated to grade IV hepatic coma despite full supportive measures. Seven of these patients regained consciousness during the period of haemoperfusion which was uncomplicated, with an average platelet drop of only 15% (range 0-30%). All finally made a complete clinical and biochemical recovery and were discharged from hospital.

**Liver Damage in Patients Taking Methyldopa**

P. J. TOGHILL, P. G. SMITH, PATRICIA BENTON, R. C. BROWN, AND H. L. MATTHEWS (Nottingham General Hospital and Derbyshire Royal Infirmary) Since 1962 there have been sporadic reports of liver damage in patients taking methyldopa. The clinical syndrome has usually resembled viral hepatitis with prompt recovery...
on stopping the drug (Elkington, Schreiber, and Conn, 1969) but there have been some fatalities from hepatic necrosis (Rehmann, Keith, and Gall, 1973). Some patients have developed active chronic hepatitis (Goldstein, Lamb, and Mistilis, 1973).

We have studied 20 patients in whom liver damage appeared to be directly related to the drug. Six patients have been seen in Nottingham and Derby Hospitals in the last three years and 14 have been traced and reviewed after reports to the Committee on Safety of Medicines. Hepatitis-like reactions occurred in 16 patients and in four of these there was a recurrence of jaundice following a second exposure to the drug. Features suggestive of active chronic hepatitis were seen in two patients. There was one death from fulminant hepatic failure and a previously undiagnosed cirrhotic died from superimposed hepatic damage.

Histological material was available in 10 cases. There was a variable spectrum of response with, in the main, a mixed inflammatory cell portal infiltrate and cholestasis. The features of chronic aggressive hepatitis regressed after stopping methyldopa.

References


Renal Failure and Site of Abnormal Renal Retention of Sodium in Fulminant Hepatic Failure

S. P. Wilkinson, V. Arroyo, H. E. Moodie, L. M. Blesend, and Roger Williams (From the Liver Unit, King's College Hospital and Medical School, London) In a consecutive series of 88 patients with fulminant hepatic failure, 61 were found to have evidence of considerable renal impairment with a glomerular filtration rate (GFR) of < 25 ml/min. This was indicative of a poor prognosis, all the patients dying, whereas in those that survived (21 patients) the GFR never fell below 40 ml/min. There was a close correlation between the development of renal failure and the occurrence of endotoxaemia. This was detected using the Limulus lysate technique only in those patients with renal failure. Serial studies in two patients showed that renal failure developed at the same time as endotoxin was first detected in the systemic blood. The underlying mechanisms may be related to selective renal vasoconstriction which endotoxin is known to cause.

Although there was renal retention of sodium in all patients with renal failure, this was also found in 10 of 25 patients with a GFR > 40 ml/min. There was no difference in GFR or renal plasma flow between these patients and those with appropriate sodium excretion, but the sodium retainers had significantly lower values for free water clearance (p < 0.001) and potassium excretion (p < 0.005), indicating that the site of abnormal sodium retention was the proximal tubule. The mechanism for this is uncertain but hyperaldosteronism is likely to be important.

Serum Ferritin in Patients with Iron Overload and with Acute and Chronic Liver Disease

J. Prieto, Michael Barry, and Sheila Sherlock (The Department of Medicine, The Royal Free Hospital, London) An immunoradiometric assay has been used to determine serum ferritin in patients with iron overload states and in patients with liver disease. In iron overload disorders serum ferritin was closely correlated with standard measurements of storage iron, namely, liver iron concentration, DTPA-chelatable iron, and the storage iron mobilised during quantitative phlebotomy. In haemolytic disorders, however, serum ferritin levels were higher, relative to the iron stores, than in patients with idiopathic haemochromatosis. High ferritin levels were common in patients with both acute and chronic liver disease, normal values being virtually confined to women and to patients with a history of recent haemorrhage. In liver disease generally serum ferritin varied with both the transaminase level and with liver iron concentration but correlated well with neither separately; however, an extremely close correlation was found between serum ferritin and the product of the serum transaminase × liver iron concentration. This is strong evidence that the ferritinaemia of liver disease is largely derived from damaged hepatocytes, the circulating level depending on both the activity of the hepatocellular damage and on the parenchymal iron stores.

Experimental Production of Lipoprotein X (LPX) in the Absence of Obstructive Jaundice

J. A. James, C. H. Bolton, and A. E. Read (University Department of Medicine, Bristol Royal Infirmary, Bristol) LPX is a unique lipoprotein found in cases of obstructive jaundice whether the obstruction be intra- or extrahepatic. It contains an abnormally high concentration of lecithin and a small proportion of phospholipid. Lithocholate is not present in other lipoproteins and is known to be hepatotoxic. In the presence of biliary obstruction, both lithocholate and lecithin may be expected to accumulate, as they are both excreted in the bile.

Using the rabbit, we have shown that when obstructive jaundice is produced artificially (by tying off the hepatic ducts), a lipoprotein similar to LPX is produced (16 cases). We then administered excess amounts of either lecithin or lithocholate to normal rabbits in order to investigate the effects of these substances. When lecithin was infused (into six rabbits) LPX appeared after 24 hours, and at no time was there any evidence of hepatic obstruction. Similarly, continuous oral administration of lithocholate (four rabbits) produced LPX after six days. There was no hepatic obstruction at this time, although it developed after 10 days.

It seems likely that lithocholate and lecithin are able to induce the formation of LPX in the absence of hepatic obstruction. We suggest that LPX may be formed as a mechanism for protecting the body from the toxic effects of lithocholate.

Primary Liver Cell Carcinoma: Alcohol and Chronic Liver Disease

Rosemarie Lucainin Fisher, P. J. Scheuer, and Sheila Sherlock (Departments of Medicine and Morbid Anatomy, Royal Free Hospital, London) A correlation between ethanol ingestion and primary liver-cell carcinoma was established in a review of 171 patients with primary liver-cell carcinoma at the Royal Free Hospital between 1960 and 1973. Fifty-six per cent were from the United Kingdom; of these, 51% had ingested more than 100 g ethanol per day and 41% more than 200 g.

Only 6% of these patients had biopsy evidence of alcoholic liver disease. However, increased ethanol consumption was significantly more common in those with carcinoma than in a population with...
cryptogenic or alcoholic cirrhosis alone. No relationship was established between carcinoma in patients with increased ethanol ingestion and hepatitis type-B antigen.

Carcinoma patients with increased ethanol ingestion showed longer survival from onset of liver disease, eg, cirrhosis, hepatitis, and a longer carcinoma-free period. Survival time from tumour diagnosis was not significantly different in patients with and without increased ethanol ingestion.

An unexpected clinical finding was an ascitic fluid protein content of less than 3 g % in 79% of the patients with carcinoma.

It appears that the relationship of primary liver-cell carcinoma and alcohol is more important than hitherto suspected.

**Effects on Prostaglandin Biosynthesis of Drugs Affecting Gastrointestinal Function**

**ALISON A. BUTT, H. O. J. COLLIER, P. J. GARDNER, AND S. A. SAEED (Research Department, Miles Laboratories Limited, Stoke Poges, Slough, Buckinghamshire)**

(Introduced by Dr J. J. Misiewicz)

Administration of E or F prostaglandins (PG) elicits nausea, vomiting, abdominal pain, and diarrhoea. The gut produces prostaglandins in response to noxious stimulation. Such evidence suggests that endogenous prostaglandins may mediate 'defensive' reactions of the gastrointestinal tract, such as vomiting and diarrhoea (Collier, 1971). We therefore tested the effects on prostaglandin biosynthesis of some drugs that affect gastrointestinal function.

Drugs were tested on (1) synthesis of prostaglandins (mainly PGE\(_2\)) from arachidonic acid by homogenate of bull seminal vesicle, with glutathione and hydroquinone as cofactors; and (2) maintenance of resting tone in an isolated strip of rat stomach fundus (Bennett, Fox, and Stamford, 1973), which is probably due to intramural generation of prostaglandin (Eckenfels and Vane, 1972). Results with the two methods were largely in agreement.

These experiments yielded the following conclusions. First, aspirin-like drugs, including paracetamol and quinoline antimalarials, inhibited PG synthesis; and their potencies overall were not correlated with ability to erode the mucosa. Second, dexamethasone had little or no activity. Third, sulphasalazine, which is useful in ulcerative colitis, was a fairly potent inhibitor of PG synthesis. Fourth, although antihistamine activity was not associated with inhibition of PG synthesis, promethazine, which is a useful antiemetic, was an inhibitor. Fifth, colchicine, whose main side effects are nausea, vomiting and diarrhoea, and apomorphine and morphine stimulated PG synthesis.

These findings suggest that inhibition by suitable drugs of prostaglandin biosynthesis in the gut wall may afford symptomatic relief in some circumstances and that the gastrointestinal side effects of certain drugs may be mediated by their stimulating such biosynthesis.

**References**


**Effects of Sulphasalazine (Salazopyrin) on Faecal Flora in Patients with Inflammatory Bowel Disease**

**R. LENDRUM, J. G. WALKER, BERYL WEST, AND M. J. HILL (From the Departments of Gastroenterology and Bacteriology, St Mary's Hospital, London)**

There is considerable interest regarding the mode of action of sulphasalazine in producing its beneficial effects in ulcerative colitis. One possible mechanism would be an antibacterial effect although previous studies have not supported this (Gorbach, Nahas, Plaut, Weinstein, Patterson, and Levitan, 1968; Cooke, 1969). Because of recent improvements in anaerobic bacteriological technique, it seemed worthwhile re-examining this hypothesis.

Faecal flora were examined by the methods of Drasar and Crowther (1970) in 21 patients with colitis and five with Crohn's disease affecting the large bowel during sulphasalazine administration and during control periods. In patients not receiving the drug, there were no differences in flora between those with Crohn's disease and those with colitis. In the latter condition patients with severe, active disease had many more opalescent-negative clostridia than the less active patients, whose flora were not significantly different from normal. The effect of sulphasalazine was to decrease the numbers of opalescent-negative clostridia 200-fold, coliforms 40-fold, and eubacteria and bacteroides 10-fold. Other organisms were unaffected. It is notable that the organisms most affected, ie, opalescent-negative clostridia, are those most active in degrading sulphasalazine.

**References**


**A Prospective Follow Up of Outpatients with ‘Total Colitis’**

J. E. LENNARD-JONES, J. J. MISIEWICZ, J. A. PARRISH, JEAN K. RITCHIE, E. T. SWARBRICK, AND C. B. WILLIAMS (St Mark's Hospital, London) The risks to patients with ulcerative colitis involving the whole colon (Edwards and Truelove, 1963; de Dombal, Watts, Watkinson, and Goligher, 1966; Watts, de Dombal, Watkinson, and Goligher, 1966) have prompted some workers to recommend colectomy for all such patients (Watts et al, 1966). We have tended to adopt a more conservative approach for outpatients with total colitis in relatively good health. To assess the results of this policy a long-term follow up of these patients was started in 1966.

One hundred and seventy-one patients have been included, 94 men and 77 women, collected from three sources: (1) 65 patients seen at St Mark's before 1 January 1966; (2) 70 patients referred with established total colitis; (3) 36 patients whose colitis became total while under our care. The mean length of follow up, so far, is 3-3 years.

The expected mortality is 4·83; seven patients have died and the excess annual mortality has been 0·3%.

Three patients have developed carcinoma. All three had premalignant rectal biopsies and were operated on because of the high risk of developing cancer, though the presence of a tumour was unconfirmed preoperatively. Two of the tumours were confined to the bowel wall, and the third showed extension through the wall with synchronous node involvement. The patients remain well seven, six, and two years after colectomy.

Twenty-nine patients have undergone colectomy; seven in an acute attack, the remainder electively. There have been no operative deaths.

The results suggest that patients with quiescent total colitis can be managed conservatively with relative safety provided that close supervision is maintained.

**References**

Mucin Changes in Colonic Mucosa in Colorectal Carcinoma

M. ISABEL FILIPE, A. C. BRANFOOT, AND B. K. COOKE (Departments of Histopathology and Chemical Pathology, Westminster Medical School, London) The large intestinal mucosa from surgical specimens of carcinoma of the colon or rectum has been studied. Histochemical techniques show differences in the mucin composition between histologically normal mucosa far from the tumour and in apparently normal mucosa adjacent to carcinoma ('transitional mucosa').

In normal mucosa, sulphomucins are predominant in the goblet cell mucus, while in 'transitional mucosa' there is a decrease in sulphomucins and a marked increase in sialomucins.

Biochemical analysis reveals a higher content of hexosamines and a higher percentage of neuraminidase-sensitive sialic acids in the 'transitional mucosa' compared with the normal and autoradiographic studies with $^{35}$SO$_4$ show a lower uptake of the isotope in the 'transitional mucosa'.

Mapping of the mucins in the large intestinal mucosa along whole specimens resected for carcinoma reveals mucin changes with increase in sialomucins, not only in areas adjacent to carcinoma, but also in patches of histologically normal mucosa distant from frank tumours. The hypothesis is put forward that these mucin changes found in histologically normal mucosa of specimens of colorectal carcinoma may represent one of the features of an early stage in carcinogenesis.

The value and application of these findings to rectal biopsies are illustrated.

Heredity and Bowel Cancer

E. LOVETT (introduced by B. C. MORSON) (St Mark's Hospital, City Road, London) There have been many reports in the literature of families with a high incidence of carcinoma of the large bowel not associated with multiple polyposis. The family histories of 209 patients admitted to St Mark's Hospital with cancer of the colon and rectum during a three-year period were investigated in detail. Information was obtained about all first-degree relatives and this was subsequently verified from death certificates or hospital records.

The number of deaths due to cancer of the large bowel was compared with the number which would have been expected by chance, as calculated from the Registrar-General's Mortality Statistics. There was a significant increase in the number of deaths due to bowel cancer among first-degree relatives of index cases compared with the expected incidence. The index cases were also analysed in respect of age, presence or absence of adenomas or other carcinomas in the operation specimen, and a history of previous carcinoma in the large bowel. Early age of onset, the presence of adenomas or other carcinomas in the operation specimen, and a history of previous carcinoma were all found to be associated with an increased risk that the index case would have a positive family history.

The relative contributions of heredity and environment to the aetiology of large bowel will be discussed.

Inhibition of Rosette-forming Activity of Lymphocytes in Patients with Large Bowel Cancer by a Colorectal Tumour Extract

M. B. MCLLMMURRAY AND M. J. S. LANGMAN (Department of Therapeutics, City Hospital, Nottingham) Thymus-derived lymphocyte (T cell) function has been explored by using the sheep red blood cell rosette test in standard and modified forms in patients with large intestinal cancer and in matched controls.

Mononuclear cells were separated from blood samples by using a Ficoll-Trisisol gradient and the proportions of rosette-forming cells were determined in the test and control groups. No differences were found between them (means and standard errors of $48.2\% \pm 2.48$ and $49.7\% \pm 1.89$ respectively).

Rosetting of patient and control cells was then repeated after preincubation with an extract prepared from a homogenate of freshly removed surgical samples of colonic and rectal tumour tissue. The ratio of rosette-forming cells with and without preincubation (termed the 'rosetting index') was significantly reduced in the cancer group but not in the controls (mean and standard errors of $0.88 \pm 0.05$ and $1.01 \pm 0.01$ respectively). Differences between patients and controls were unrelated to tumour extent as determined at operation. The results suggest that altered T cell function of specific type is detectable by relatively simple means in patients with intestinal cancer and are in broad agreement with lymphocytotoxicity assays and leucocyte migration inhibition studies (Guillou and Giles, 1973; McIlmurray, Gray, and Langman, 1973).

References


An Experimental Animal Model of Crohn's Disease

D. R. CAVE AND D. N. MITCHELL (Department of Surgery, St George's Hospital, London, MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, London) The terminal ileum or proximal colon of 19 New Zealand White rabbits (NZW) was inoculated intramurally with a 100μl or 0.2μl filtrate of homogenate prepared from fresh human ileal or colonic Crohn's disease tissue. When compared with nine inoculated controls, the Crohn's inoculated rabbits gained weight at a significantly slower rate ($p < 0.001$ at seven weeks). Macroscopic changes were present in 15 of 19 Crohn's inoculated rabbits and were independent of the nature or donor of the Crohn's filtrate homogenate or the site of inoculation. Positive microscopic changes were present in eight of 19 Crohn's inoculated rabbits. No macroscopic abnormalities were present in any of the nine control inoculated rabbits and microscopically all were negative. Successful first passages have been achieved from rabbits given 100μl or 0.2μl filtrate of human Crohn's homogenate prepared from each of five different donors. The results of these experiments provide further evidence to support the presence of a transmissible agent from human Crohn's disease tissue, and illustrate the potential of the NZW rabbit as an experimental model with which to study the aetiology and natural history of Crohn's disease in man.

Antibody Production to the Bacteriophage aα 174 in Patients with Crohn's Disease

R. C. BUCKNALL, J. VERRIER JONES, AND
been used and has been with an incidence from surveys.

Disease in the Incidence of disease raise, within the Department of University (Department of University). Jones, and Gough, M. (1973). One patient (C2) had high levels of circulating antibody before immunization: this has never been observed in normal subjects. The remaining patients had primary responses within the normal range. A second injection of bacteriophage was given on day 28. The patient C2 had no further increase in titre. The remaining patients developed a normal secondary response. The antibody from the peak of the initial response in C2 was of IgG subclass. A further group of five patients with Crohn's disease was screened for preimmunization antibody, and all were found to be negative.

Our observations show that the depression in cellular immunity found in Crohn's disease is not accompanied by a depression of antibody producing capacity.

Reference

The Incidence and Prevalence of Crohn's Disease in the Nottingam Area

D. S. MILLER, A. C. KEIGHLEY, E. M. BACKETT, AND M. J. S. LANGMAN (Nottingham)
Applying diagnostic criteria which have been based upon those used in previous epidemiological surveys we have examined trends in the frequency of diagnosis of Crohn's disease in the Nottingham area in the period 1958-1972. The figures have been used to calculate incidence and prevalence rates. During this time there has been a marked and consistent increase in the frequency of disease diagnosis with an apparent rise in incidence from 0-34/100 000/year for men and 1-05/100 000/year for women in 1958-61 to 2-61 and 3-73 respectively in 1968-72.

These results have been compared with those obtained by the Hospital Inpatient Enquiry where similar trends have been observed. Comparison with the admission rates for ulcerative colitis shows a much smaller increase over the same period and provides no evidence to suggest that transfer of colitis to Crohn's disease diagnoses is the predominant cause of this apparent rising frequency of Crohn's disease. Furthermore analysis of our own data shows that the proportion of small to large bowel Crohn's disease has not varied in the time period reviewed.

Oral Lesions in Patients with Crohn's Disease

M. K. BASU, F. AQUITH, R. A. THOMPSON, AND W. T. COOKE (Department of Oral Pathology and Experimental Pathology, University of Birmingham, Regional Immunology Laboratory, East Birmingham Hospital, and the Nutritional and Intestinal Unit, The General Hospital, Birmingham)

Oral lesions with characteristic histology have been described in patients with Crohn's disease (Ellis and Truelove, 1972) while a retrospective study of 332 patients with Crohn's disease showed that 6-1% had suffered with oral ulceration (Croft and Wilkinson, 1972). A prospective study of 100 patients with Crohn's, 100 with ulcerative colitis, and 100 age-, sex- and denture-matched controls showed that nine Crohn's, two ulcerative colitis', and one control subject had oral lesions. Histologically the Crohn's lesions showed similarities to those seen in the intestine and could be correlated with activity of bowel disease but not with deficiency of iron, vitamin B12, or folic acid. Changes were also found in minor salivary glands. The occurrence of oral lesions might represent a local immunological reaction to oral antigens. In support of this, changes in salivary IgA production were found in Crohn's patients.

References

The Results of Outpatient Treatment of Haemorrhoids by Rubber Band Ligation

A. P. PANDA, J. M. LAUGHTON, J. B. ELDER, AND I. E. GILLESPIE (University Department of Surgery, The Royal Infirmary, Manchester)

Few follow-up assessments of elastic ligation of haemorrhoids have been published (Clark Giles, and Goligher, 1967; Groves, Evans, and Williams, 1971). Seventy-five patients with symptomatic haemorrhoids have been treated as outpatients by rubber band ligation without anaesthesia using the technique of Barron (1963). Their ages ranged from 25 to 75 years. Each patient had a sigmoidoscopy and a barium enema before ligation. On average, three ligations on separate days were required for each patient and follow up has been from six to 26 months with an average of 10 months after the completion of treatment.

RESULTS
Sixty-five patients returned to work less than 24 hours after ligation, eight within 48 hours, and two at more than 48 hours. During the first week 36 were completely asymptomatic, 26 had minimal discomfort, and 13 had moderate pain with a sense of incomplete evacuation in the rectum and some frequency of call to stool in one patient lasting seven days. No patient required hospitalization for either rectal bleeding or pain immediately after ligation.

Long-term follow up was possible in 68 of 75 patients, only seven remaining untraced. In 60 there was no rectal bleeding, in six occasional bleeding, and in two regular bleeding during defaecation. Six patients required and consented to re-ligation of residual haemorrhoids and two elected to have a formal haemorrhoidectomy.

We conclude that outpatient ligation treatment of haemorrhoids is a successful procedure, conferring the benefits of early return to work and minimal discomfort in the vast majority of patients with a low incidence of recurrence of rectal bleeding. Outpatient waiting time for treatment of haemorrhoids has been considerably reduced and hospital beds have been freed for other cases.

References

The Diagnosis of Pseudomembranous Colitis by Rectal Biopsy

A. B. PRICE AND D. R. DAVIES (St Mark's Hospital, London and St Thomas' Hospital, London) (introduced by B. C. MORSON)
It is important to make a rapid diagnosis in all cases of pseudomembranous colitis as the majority of these patients are severely ill. However, clinical and radiological distinction from the acute forms of ulcerative colitis and Crohn's disease of the colon is usually very difficult. Furthermore, as conservative management, where possible, is the treatment of choice, a quick and accurate assessment is required.

The rectal biopsy appearances of six cases of pseudomembranous colitis are described. The features are characteristic and easily distinguishable from other causes of inflammatory bowel disease, especially Crohn's disease and ulcerative colitis. However, in four of these cases the initial report was given as non-specific proctitis or 'compatible with ulcerative colitis'. This indicates the need for more widespread recognition of the typical rectal biopsy appearances of pseudomembranous colitis. A confident diagnosis can be made by sigmoidoscopy and rectal biopsy, and we feel biopsy should be performed early in those patients with diarrhea, in whom pseudomembranous colitis comes into the differential diagnosis; notably diarrhea associated with antibiotic therapy, shock, transfusion reactions, subacute colonic obstruction, and chronic cardiac and renal states. Such predisposing factors, in particular antibiotic therapy, are discussed in the light of recent publications (McGovern, 1972; Scott, Nicholson, and Kerr, 1973).

References

Gas Chromatographic Measurement of Mucopolysaccharides in Gastric Juice of Patients with Duodenal Ulceration
J. D. Donaldson, K. D. Macrae, T. G. Parks, and H. W. Rodgers (Department of Surgery, Queen's University, Belfast)
Measurement of gastric acid and pepsin output is of limited value in the diagnosis of duodenal ulceration. Possible abnormalities of the mucopolysaccharides in gastric juice have not been fully explored. This study examines differences in the sugar constituents by gas liquid chromatography in basal and pentagastrin-stimulated juice between 42 duodenal ulcer patients and 22 control subjects.

In duodenal ulceration the concentration of fucose, mannose, galactose, glucosamine, and galactosamine differed significantly from normal in at least one specimen. In particular the content of free and total sialic acid was distinctly abnormal (p < 0.05). Using multivariable discriminant analysis incorporating the three features, it was possible to distinguish clearly between ulcer patients and controls with 96.8% accuracy, whereas differentiation on the basis of the pentagastrin stimulation test of hydrochloric acid output was only 53.7%.

In 12 duodenal ulcer patients who subsequently came to surgery the preoperative mucopolysaccharide level was abnormal in all cases whereas only five of these had acid levels above the normal range.

It is concluded that analysis of the sugar constituents of gastric juice, although time consuming, is potentially an accurate method for the diagnosis of duodenal ulceration.

Osmotic, Electrolyte, and pH Changes in the Human Jejunum after Truncal Vagotomy and Drainage
J. G. Temple, A. M. Birch, and R. Shields (Department of Surgery, Liverpool)
Comparatively little is known about the composition of the proximal jejunal content after a meal in health or disease (Fordtran and Locklear, 1966).

Fasting subjects ingested a 300 ml hyperosmotic meal (600 mOsm/kg) containing EDTA 41Cr as a volume marker. Samples were collected at 30-minute intervals for two and a half hours by siphonage through a single-lumen polyvinyl tube whose tip was placed in the proximal jejunum.

Three groups of subjects were studied: (1) 12 controls, (2) 11 patients without diarrhea after vagotomy and drainage, and (3) 10 patients with postvagotomy diarrhea.

Analysis of the jejunal content revealed: (1) There was no evidence that a hyperosmotic load or excessive dilution was present in the small bowel in patients with postvagotomy diarrhea. (2) All the postvagotomy subjects showed a greater rise in sodium concentration than the controls in the first hour after the meal. (3) Subjects with postvagotomy diarrhea had significantly greater sodium concentrations than the symptom-free subjects at all times after the first 30 minutes. (4) Chloride concentrations rose slowly towards plasma values in each group. (5) Patients with diarrhea had higher pH values than the other two groups at all times.

These findings challenge some of the current concepts concerning the aetiology of postvagotomy diarrhea.

References

The Predictive Accuracy of the Insulin Test after Vagotomy: A New Interpretation
R. G. Faber, R. C. G. Russell, J. V. Parkin, P. Whitefield, and M. Hobley (Department of Surgical Studies, The Middlesex Hospital, London) By conventional criteria, the postvagotomy insulin test poorly predicts the liability to recurrent peptic ulcer. All criteria depend upon comparison between basal and stimulated secretion (Hollander, 1948; Bank, Marks, and Louw, 1967), but we have shown that basal secretion is physiologically variable. Therefore in 29 preoperative and 71 postvagotomy male patients with duodenal ulcer, the predictive accuracy of insulin-stimulated (0-2 units/kg iv) secretion alone has been investigated. Corrections for pyloric loss (Hobsley and Silen, 1969) and duodenal reflux (Fiddian-Green, Russell, and Hobsley, 1972) have been made to the observed volume, the resultant true gastric secretion being designated Vo.

Insulin-stimulated secretion was measured for two hours. Before operation, the rate during the first half-hour was much lower than in the subsequent one and a half hours. Moreover, the timing of the peak secretion was very variable. Vo throughout the period half to two hours has therefore been chosen as the index of insulin-stimulated secretion, and expressed as ml/hour. The mean preoperative value was 215 ml/hour.

After vagotomy, 54 subjects secreted less than 116 ml/hour (preoperative mean minus twice the standard deviation); none had a recurring ulcer. However, of 17 subjects secreting more than 116 ml/hour, five had recurrent ulcer, four had recurrent symptoms, and only four (two within one year of operation) were symptom free.

We conclude that insulin-stimulated secretion alone predicts recurrent ulceration more accurately than any other criterion.

References
Characterization of Glucagon Responses to Different Meals in the Dumping Syndrome

F. A. O'Connor, K. D. Buchanan, E. R. Trimble, J. R. Hayes, and T. L. Kennedy (Departments of Medicine and Surgery, The Queen's University of Belfast, Northern Ireland) High levels of glucagon-like immunoreactivity (GLI) after oral glucose have been reported in the dumping syndrome. In order to decide whether these GLI responses are due to the release of pancreatic glucagon or to the as yet uncharacterized gut GLI, we have studied the GLI responses to 50 g oral glucose in 20 'dumpers' using two antibodies in the glucagon radioimmunoassay which allow discrimination between gut GLI and pancreatic glucagon. The GLI responses to a 25 g protein meal and a 50 g fat meal have also been studied in 'dumpers'. Gut GLI rose in 'dumpers' no matter whether the meal was glucose, fat, or protein (p < 0.005, < 0.05, < 0.05 respectively) and the rises exceeded that of control subjects. Abnormalities in pancreatic glucagon responses to the meals also occurred in the 'dumpers' in that pancreatic glucagon paradoxically rose after glucose in seven out of 15 'dumpers' compared to suppression (p < 0.05) in control subjects. A rise in pancreatic glucagon to fat was also found in the 'dumpers' (p < 0.05), but in contrast the pancreatic glucagon response to protein in the 'dumpers' was deficient compared with controls. These abnormalities of pancreatic glucagon and gut GLI release in 'dumpers' may have either a compensatory or causative influence on the various features of 'dumping', including rapid gastric emptying, diarrhoea, and hypoglycaemia.

Reference


Effects of Varying Degrees of Vagotomy on the Gastroduodenal Response to Food

G. J. Stoddard and H. L. Duthie (University Surgical Unit, Royal Infirmary, Sheffield) We have previously shown that bursts of action potentials (APs) known as myoelectrical complexes (Szurszewski, 1969), which pass down the small intestine of fasting dogs, are disrupted following vagotomy, the extent of these changes being related to the amount of vagal denervation (Stoddard and Duthie, 1973). The paper reports the alterations that occur in response to feeding after vagotomy.

Six Ag-AgCl electrodes were attached to the stomach and duodenum of four dogs and three-hour recordings of the myoelectrical activity made following a meal test. Following pyloroplasty and further testing one dog received a truncal vagotomy (TV) and the three others a highly selective vagotomy followed four weeks later by TV.

In all tests feeding produced immediate interruption of the myoelectrical complexes and their replacement with gastro-duodenal APs. Before pyloroplasty during the first hour after food, 98-82% ± 0.50 of gastric pacesetter potentials had APs which were coordinated with SPs in the proximal duodenum. Other APs not coordinated with antral APs are seen most frequently in the distal duodenum.

The incidence of gastric APs decreases and uncoordinated duodenal APs increases in the following two hours until normal myoelectrical complexes return.

Pyloroplasty or HSV do not alter gastro-duodenal coordination of APs. On the other hand TV was followed by a significant increase in duodenal APs which were not coordinated with gastric APs. Preservation of the vagal innervation to the antro-duodenal segment after HSV maintains normal gastro-duodenal coordination of APs.

References


The Influence of the Innervated Gastric Antrum on Gastrin and Acid Responses to Insulin Hypoglycaemia in Man

P. J. Lyndon, J. H. Walsh, and D. Johnston (University Department of Surgery, Leeds General Infirmary, and Department of Medicine, UCLA, California) The hypothesis upon which highly selective vagotomy (HSV) is based is that the vagally innervated gastric antrum will not release excessive amounts of gastrin in response either to vagal or to chemical stimulation. The response to a test meal after HSV has been described previously to the Society (Lyndon, Walsh, Johnston, and Grossman, 1973). We have now tested the basic hypothesis by measuring serum gastrin levels by radioimmunoassay, and gastric acid outputs after vagal stimulation in preoperative duodenal ulcer patients (DU), and in patients who had undergone HSV, truncal vagotomy and pyloroplasty (TV + P), or selective vagotomy and pyloroplasty (SV + P) more than one year previously (n = 12 in each group). The stimulus used was insulin hypoglycaemia. Vagotomized patients were in good health, and in each the vagotomy had been shown to be complete soon after operation.

Mean (±1 SE) fasting gastrin levels in pg/ml were 70 ± 5 (DU), 107 ± 11 (HSV), 91 ± 7 (TV + P), and 91 ± 8 (SV + P). Mean peak gastrin levels were 81 ± 7 (DU), 114 ± 13 (HSV), 114 ± 13 (TV + P), and 134 ± 19 (SV + P). There was no significant difference between the gastrin levels or the acid levels after HSV compared with those after TV + P or SV + P. However, the mean peak acid response in 18 patients more than two years after HSV (3·7 m-equiv/hr) was significantly greater than the peak acid response in 37 patients more than two years after TV + P (1·40 m-equiv/hr, p < 0·002 by the Mann Whitney U test). Also, more than two years after operation, 90% of 18 patients after HSV had Hollander positive responses to insulin compared with 68% of 37 patients after TV + P.

Reference