Gut, 1971, **12**, 853-870

The British Society of Gastroenterology

The 32nd annual general meeting of the British Society of Gastroenterology was held at Newcastle upon Tyne from 23 to 25 September 1971 under the Presidency of Professor A. A. Harper. The programme included the abstracts that follow and in addition symposia on 'Aetiology and epidemiology of carcinoma of the colon and rectum' and 'Ischaemic colitis', and a progress report by Professor E. L. Blair on 'Measurement of gastrointestinal hormones'. A report on the business of the meeting is printed on page 871.

Gastroenterostomy—An Obsolete Operation?

W. P. SMALL, C. W. A. FALCONER, A. N. SMITH, J. P. A. MCMANUS, AND W. SIRCUS (*Gastro-Intestinal Unit, Western General Hospital, Edinburgh*) Gastroenterostomy fell from favour once its association with a high incidence of jejunal ulceration became recognized. It has never regained popularity, although some surgeons have recommended its further trial (Tanner, 1969) and although surgeons who could look back to the heyday of gastroenterostomy claimed that, when uncomplicated by jejunal ulcer, its results as measured by absence of side effects have never been bettered (Farquharson, 1956).

In the last 14 years, gastroenterostomy has been used in this Unit as part of a selective policy for those patients with low levels of acid output (Small *et al*, 1967). One hundred and thirty-six patients with duodenal ulcer have to date been treated by gastroenterostomy and 18 of these have been followed for more than five years. The series has been subject to careful periodic review. Apart from one patient who developed jejunal ulcer within 11 months, no other case of jejunal ulcer has been encountered in the select group. The evidence begins to support the claim that gastroenterostomy can be a safe operation in terms of freedom from risk of jejunal ulcer. There is also confirmation of the belief that successful gastroenterostomy has benefits to the patient in terms of a reduced incidence of dumping, diarrhoea and bile vomiting.

It is concluded that gastroenterostomy is an operation worthy of its place in the surgical treatment of duodenal ulcer, provided its use is restricted to those patients having a low acid output.

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Preparation and Characterization of Lateral and Basal Plasma Membranes of the Rat Enterocyte

A. P. DOUGLAS, R. KERLEY, R. CORNELL, AND K. J. ISSELBACHER (*Royal Postgraduate Medical School, University of London, London, W.12, and Massachusetts General Hospital, Boston, USA*) Anatomical and physiological studies suggest there is a distinct polarity in the enterocyte. These considerations suggest there may well be differences between the plasma membrane (PM) of the brush border and that of the lateral and basal boundaries of the cell. A method has been developed in our laboratory (*Biochem. J.*, **106**, 381, 1968) for preparation of microvillus membranes and we now describe the preparation of PM derived from other parts of the enterocyte. Isolated intestinal epithelial cells from the rat are homogenized by nitrogen cavitation. By a combination of differential centrifugation and separation on sorbitol and dextran gradients a fraction has been isolated which is predominantly PM. It contains less than 0·5% of the initial sucrase activity and none of those enzyme activities associated with mitochrondria. Electron microscopy shows the final preparation consists entirely of smooth membranes and enzyme data allows the conclusion that less than 15% of these membranes are derived from endoplasmic reticulum. The final preparation contains 9% of the initial alkaline phosphatase and 10% of the initial (Na^+, K^+)-ATPase with a 10-fold purification of these PM markers.

The ability to prepare lateral PM as well as microvillus membrane from the enterocyte should enable further understanding to be reached of the functional polarity of that cell.

The Breakdown of Dietary Cellulose in Man

G. J. MILTON-THOMPSON AND B. LEWIS (*Research Department, St. Mark's Hospital, London, E.C.1*)

Although cellulose is a major nutritional source in herbivorous animals, there is disagreement about cellulose breakdown in the gastrointestinal tract of man.

A simple analytical method for the isolation of cellulose from foodstuffs and faeces by digestion with nitric and acetic acids (Crampton and Maynard, 1938) has been adapted to performing cellulose balance studies in man.

Sixteen normal subjects have been studied under controlled conditions on a standard full diet containing a fixed intake of cellulose (8·5 g per day) and using cuprous thiocyanate as a continuous marker (Dick, 1969). Mean recovery of ingested cellulose from faeces was 43% with a range of 15% to 87%.

The significance of these findings in relation to nutrition and to the laxative effect of high residue diets will be discussed.

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Ultra-active Treatment of Haematemesis and Melaena

M. ELIZABETH M. STEPHENS, S. HAYNES, D. B. MACKIE, H. B. MCMICHAEL, T. D. KELLOCK, AND F. AVERY JONES (*Central Middlesex Hospital, London*) There has been negligible improvement over the past fifteen years in the survival rate following gastrointestinal bleeding (Schiller, Truelove and Gwyn Williams, 1970). There has, however, been a great increase in our understanding of shock (*Brit. J. Hosp. Med.*, 1968). Central venous pressure (CVP) monitoring is useful as an early warning of rebleeding (Northfield and Smith, 1967), but is also the keystone to fluid therapy in shock.

We studied, in one year, 88 patients with gastrointestinal bleeding, who were over 60 years old and therefore at high risk. We were able, by CVP monitoring, not only to correct hypovolaemia in a few minutes, but also, with the use of adequate diuretics, to correct anaemia rapidly in all patients (eg, transfusion of 6 pints of blood in six hours to a patient not actively bleeding and initially in heart failure). The potential advantages of such therapy are discussed.

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The Influence of Amino Acids on Sodium and Water Absorption from the Small Intestine

M. D. HELLIER, C. D. HOLDSWORTH, AND C. THIRUMALAI (*The Medical Unit, St. Bartholomew's Hospital, London, and The Royal Infirmary, Sheffield*) In man it has been established that there is little absorption of sodium or water from solutions of isotonic sodium chloride in the jejunum unless an actively transported sugar such as glucose is present (Sladen, 1969). We have used a perfusion technique in man to study the effects of amino acids and dipeptides on sodium and water absorption.

Although there was no significant absorption of sodium or water from normal saline solutions, absorption was stimulated by the presence of either glycine or alanine at concentrations of 10 mMolar, and increased progressively as this was increased to 20 mMolar and 50 mMolar.

Absorption of sodium and water was also stimulated by the presence of the dipeptide glycyl-glycine. The effect of 25 mMolar glycyl-glycine and 50 mMolar glycine on sodium and water absorption was the same, despite the fact that glycine absorption was much greater from the dipeptide solution. Thus although the dipeptide confered a kinetic advantage on glycine absorption, this was not reflected by a corresponding increase in sodium and water absorption, and suggests that the site of interaction between sodium and amino acids may be superficial to the site of dipeptide hydrolysis.

Stimulation of sodium and water absorption by amino acids has also been demonstrated by parallel *in vivo* studies in rats.

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Effects of Prostaglandin E_1 on Net and Unidirectional Movements of Water and Electrolytes across the Jejunal Mucosa in Man

C. MATUCHANSKY AND J. J. BERNIER (*Groupe de Recherches sur la Physiopathologie de la Digestion—Inserm.—Hopital Saint-Lazare, 107, rue du Fg-St-Denis, 75. Paris* 10°) Prostaglandins have a powerful diarrhoeal action (Misiewicz, Waller, Kiley, and Horton, 1969), but their effects on small intestinal transport of fluid and electrolytes have not been, so far, investigated in man. In this work, the effects of intrajejunal prostaglandin E_1 (PGE_1) upon the mean transit time (MTT), net and unidirectional movements of water and electrolytes were studied in

the human jejunum by an intestinal perfusion technic with a four-lumen tube: 10 normal subjects were perfused, each one being his own control. The infused solution contained: NaCl 100 mM, mannitol 100 mM, PEG 10 g, ^{22}Na 4 μc; HTO 100 μc per litre: the rate of perfusion was 10 ml/min.

The results show that PGE_1 significantly decrease the hydroelectrolytic absorption rate across the mucosa by inducing a considerable net secretion of water, sodium, chloride, potassium, and bicarbonate into the lumen. The blood-to-lumen unidirectional flux of HTO and ^{22}Na was strikingly increased whereas the opposite flux did not significantly change. The effect of PGE_1 on hydroionic movements were similar, whether the MTT through the perfused segment was shortened (4 cases) or not (6 cases).

These results demonstrate that PGE_1 may directly act on jejunal transport of fluid and electrolytes in man; its effects on unidirectional fluxes of water and sodium resemble those of cholera exotoxin, confirming that these agents may act upon a common intestinal secretory mechanism, as recently suggested in the dog by Pierce, Carpenter, Elliott, and Greenough (1971).

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Effects of Bile Acids on Small Intestinal Absorption of Glucose, Water, and Sodium

J. T. HARRIES AND G. E. SLADEN (*Department of Gastroenterology, St. Bartholomew's Hospital, London, E.C.1*) Unconjugated dihydroxy bile acids inhibit colonic absorption of water and sodium in several species (eg, Mekhjian and Phillips, 1970), but no detailed information is available about comparable effects in the small intestine. Previous results obtained with *in vitro* material (eg, Pope, Parkinson, and Olsen, 1966) may not be relevant to absorption *in vivo* (see Gracey, 1971).

In this study, the effects of several bile acids on absorption by the rat small intestine were investigated, using an *in vivo* closed-loop technique. Isotonic solutions, containing mainly NaCl and (in jejunum) 20 mM glucose, were placed in loops of jejunum and ileum for short absorption periods. A weighing technique was used to calculate absorption rates.

In the jejunum, deoxycholate (1 mM) impaired absorption of both sodium and water ($P = 0.002$), but not glucose. At higher concentrations (2·5 and 5 mM) secretion of fluid occurred, whereas glucose absorption was only slightly impaired ($P = 0.05$). By contrast in the ileum, 5 mM deoxycholate produced only partial ($P = 0.002$) inhibition of fluid absorption and 10 mM was needed to cause complete inhibition. In both jejunum and ileum, chenodeoxycholate behaved in a similar fashion, whereas the conjugated taurodeoxycholate (5 mM) had no significant effect.

Thus, unconjugated dihydroxy bile acids inhibit absorption of water and sodium by the small intestine. The jejunum is more sensitive than the ileum and secretes fluid even when glucose is being absorbed.

This dissociation suggests that the mucosa is not grossly damaged and is reminiscent of the changes observed in cholera. These findings may be relevant to the production of fluid diarrhoea in conditions of bacterial overgrowth in the small bowel.

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The Mechanism of Intestinal Uptake and Transcellular Transport of IgG in the Neonatal Rat

E. A. JONES AND T. A. WALDMANN (*National Institutes of Health, Bethesda, Maryland*) The mechanism of intestinal uptake and transcellular transport of plasma proteins has been studied in 14-day-old rats using intraduodenally administered radioiodinated proteins. Appreciable quantities of mouse IgG and all four subclasses of human IgG were taken up by the intestinal wall and transported to the animal, whereas there was little or no uptake or transport of human IgM, IgA, IgD, IgE, albumin, transferrin, and ceruloplasmin. Both the uptake and transport of labelled IgG were significantly inhibited by unlabelled IgG. An appreciable proportion of the label of IgG in intestinal wall homogenates, but not in plasma or intestinal washings, migrated in a sucrose ultracentrifugation gradient much more rapidly than did the administered 7S molecules. This apparent binding of labelled IgG was also markedly inhibited by unlabelled IgG. In subcellular fractionation studies of intestinal homogenates the complexed labelled-IgG was shown to be associated predominantly with cell membrane rather than cell sap fractions. It is concluded that in the neonatal rat both intestinal uptake and transport of IgG are specific saturable processes, which are associated with complexing of IgG molecules probably with membranes. The data are consistent with the

existence of specific receptors for IgG on enterocyte microvillus membranes.

Inhibition of Sugar Transport by Cystic Fibrosis Plasma

G. A. BROWN, A. OSHIN, M. C. GOODCHILD, AND C. M. ANDERSON (*Institute of Child Health, University of Birmingham*) An unidentified factor in serum, sweat, and saliva from patients with cystic fibrosis has the property of modifying epithelial function. Ciliostasis, inhibition of sodium transport, and inhibition of alanine transport have been induced in animal tissues by treatment with one or other of these fibrocystic fluids. In this paper we describe inhibition of active sugar transport by fibrocystic plasma.

Inhibition was demonstrated *in vitro* in a rat jejunal preparation using the glucose analogue arbutin. Percentage inhibition was estimated by measuring arbutin transport in the presence of plasma and relating it to transport in a plasma-free medium (100%).

Minor inhibition was seen in some control adults and children. Inhibition in fibrocystic children was much greater with little overlap with controls. Inhibition in the parents (presumed heterozygotes) of the fibrocystic children occupied an intermediate position overlapping both controls and fibrocystics.

Mean inhibition levels measured in 22 controls, 45 parents, and 28 fibrocystic children were 5·3%, 14·2%, and 24·3% respectively. Inhibition in the heterozygote at approximately half the homozygote level suggests that the transport inhibiting activity is closely related to the genetic defect.

Investigation of the factor's properties suggests a macromolecular identity with activity segregating with the albumin fraction on Sephadex gel filtration. Further investigations are in progress.

Sugar Absorption Studied by an Exsorption Technique

A. T. R. AXON (introduced by B. Creamer) (*St. Thomas' Hospital, London*) Sugar absorption has been examined in a new way by measuring the rate at which different monosacharrides may pass from the blood stream into the intestinal lumen (exsorption). Non-actively absorbed sugars exsorb in a linear fashion, the rate being proportional to plasma concentration. Actively absorbed sugars on the other hand do not exsorb at normal or even at high plasma concentrations. If however, the concentration is increased even higher, exsorption does occur and increases rapidly until it equals or exceeds that of the non-actively absorbed sugars.

The absence of sodium from the luminal fluid does not affect the exsorption of actively absorbed sugars. The presence of other actively absorbed sugars or phlorizin M $\times 10^{-2}$ in the lumen causes the pattern of exsorption to change so that it resembles that of the non-actively absorbed sugars.

These findings may be explained on the basis of a mobile carrier. The implications of this in the concept of sugar absorption will be discussed.

Preoperative Prediction of Success or Failure of Gastric Surgery

I. MCCOLL, J. E. DRINKWATER, I. HULME-MOIR, AND S. P. B. DONNAN (*St. Bartholomew's Hospital, London*) Previous attempts to predict the result of gastric surgery by Thoroughman and his colleagues (1964) were encouraging but involved somewhat complex and difficult psychological testing. In 48 patients with peptic ulcers we have attempted to predict the result of surgery using three psychological parameters: total deprivation score, maternal affection, and Eysenck personality inventory (EPI). The latter is in the form of a questionnaire which measures neuroticism/stability, extroversion/introversion and includes a lie scale. We have also tried to predict which patients will dump by measuring their sensitivity to increasing partial pressure of carbon dioxide in alveolar air (Borgström) and their sensitivity to hypertonic glucose injected into the jejunum (Fenger).

After an interval of one year the results of surgery were assessed as success or failure and a good correlation was found between the results and the psychological indices. In 32 patients in which success was predicted there were 20 successes; in 16 patients in which failure was predicted there were 10 failures (Chi square 7·6, $P < 0·01$). Attempts to predict dumping, however, were unsuccessful.

These predictions are sufficiently accurate to provide some indication of the advisability of surgery, especially in patients with intractable ulcer pain but no complications such as haematemesis, perforation, or pyloric stenosis.

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Genetic Factors in the Development of Duodenal Ulcer in Childhood

R. H. JACKSON (introduced by I. D. A. Johnston) (*Children's Department, The Royal Victoria Infirmary, Newcastle upon Tyne*) This paper reports the

results of an attempt to assess the importance of genetic factors in the development of duodenal ulcer in childhood. Two approaches were used: firstly, a family tree has been drawn up of 44 families each containing a child with a duodenal ulcer, and the frequency of ulceration among the different degrees of relatives established. Secondly, blood and saliva samples were taken from propositus and first degree relatives and the genetic markers analysed. Similar studies were done on 35 control families matched by sex, age, and social status with the ulcer family.

Blood studies have confirmed an excess of group O among the ulcer cases, but not an excess of non-secretors. No other significant differences between the two groups was found among the genetic markers studied.

The family studies have shown marked differences between the two groups with a statistically significant increase in ulcers among relatives of ulcer patients in all degrees of relationship, especially among male relatives of male propositi. Calculation of the heritability gives a figure of 0·91, a high result, showing that the genetic component in the development of duodenal ulcer in childhood is greater than that in, for example, congenital pyloric stenosis.

Some Genetic Aspects of Coeliac Disease and Dermatitis Herpetiformis

J. MARKS, D. F. ROBERTS, E. H. WYATT, S. SHUSTER, J. MACDONALD, A. J. WATSON, D. C. ROBINSON, AND D. A. BIRKETT (*From the Departments of Dermatology, Pathology and Paediatrics and the Laboratory of Human Genetics, University of Newcastle upon Tyne*) We have reported that the structural abnormalities of the upper small-intestinal mucosa seen in patients with dermatitis herpetiformis (D.H.) are common in members of the patients' families[1] though the rash of dermatitis herpetiformis is only rarely familial.

We have compared the incidence of these abnormalities with those in relatives of children with coeliac disease and have found that there is a significant difference between the two, the incidence being greater in relatives of patients with D.H. All previous evidence on the enteropathy of dermatitis herpetiformis had suggested that it was identical with that of coeliac disease[2] and so we set out to examine the genetic aspect further by determining 13 genetic markers in patients with dermatitis herpetiformis and their relatives, and patients with coeliac disease and their relatives. The number of patients examined is still relatively small but we have found a significantly higher incidence of blood group A in the patients with coeliac disease than in patients with D.H. and a significantly higher incidence of haptoglobin 1:1 homozygotes in the patients with D.H.

These results may mean that the enteropathy of D.H. is after all distinct from that of coeliac disease but could equally well mean that it is only in a special genetic sub group of coeliacs that D.H. occurs. The fact that there appears to be a genetic factor in the rash as well as in the enteropathy of D.H. also has to be taken into account in interpreting the results.

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Diagnostic Tests for the Stagnant Loop Syndrome

T. C. NORTHFIELD, B. S. DRASAR, AND J. T. WRIGHT (*Departments of Medicine and Biochemistry, Guy's Hospital Medical School, Wright-Fleming Institute, St. Mary's Hospital and Department of Gastroenterology, London Hospital, London*) The object of this study has been to determine the most useful diagnostic test for the stagnant loop syndrome, when investigating a patient with steatorrhoea. We have compared the information obtained from two non-invasive techniques (urinary indican excretion and Schilling test plus intrinsic factor) with that obtained from two intubation techniques (jejunal bacterial and bile salt patterns). We have studied 13 patients with a radiologically demonstrated stagnant loop; the patients were divided into two groups according to whether or not they had steatorrhoea attributable to the stagnant loop syndrome. The postprandial jejunal bile salt pattern proved the most useful diagnostic test. Bile salt deconjugation was demonstrated in the upper jejunum of seven out of eight patients with the stagnant loop syndrome, but not in the other patients studied, nor in 11 normal subjects. Deconjugation was demonstrated in the lower jejunum of the eighth patient with the stagnant loop syndrome, but also, to a lesser degree, in two out of 11 normal subjects. With jejunal bacteriology, there was more overlap between the patients with the stagnant loop syndrome and the normal subjects, and the other two tests showed poor discrimination between the two groups of patients studied.

Intrajejunal Volatile Fatty Acids in Gastrointestinal Disease

A. J. CHERNOV AND D. GOMPERTZ (Introduced by C. C.

Booth) (*M.R.C. Intestinal Malabsorption Research Group, Department of Medicine, Royal Postgraduate Medical School, University of London, London W.12*) The small intestine has a small but significant anaerobic flora. This is greatly increased in both the stagnant loop syndrome and during reflux contamination from the large bowel. Anaerobic organisms are characterized by fermentation reactions leading to the volatile fatty acids, acetic, propionic and butyric acids. This investigation has involved the measurement of these volatile acids in healthy subjects, in patients with clinical and/or bacteriological evidence of small bowel anaerobic infection and in patients with gastrointestinal disease without anaerobic overgrowth.

Preliminary studies demonstrated raised intraluminal acetate and propionate concentrations in both patients with the stagnant loop syndrome and patients with reflux from the large intestine. The measurement of acetate differentiated these patients from normal persons and from the group of patients with no evidence of anaerobic overgrowth. There appears to be a more consistent relationship between a raised intraluminal acetate concentration and the presence of an anaerobic infection than the presence of steatorrhoea, or B_{12} malabsorption. Treatment of three patients with the stagnant loop syndrome with antibiotics was associated with the return of elevated acetate and propionate concentrations to normal. Butyrate concentrations were raised less often but showed a similar response to antibiotic treatment. It appears that the intraluminal acetate concentrations might be a useful biochemical measure of the degree of anaerobic colonisation of the small bowel.

Fatal Malabsorption Unresponsive to Gluten-free Diet in the Adult

D. J. EVANS AND C. C. BOOTH (*Departments of Pathology and Medicine, Royal Postgraduate Medical School, University of London. London, W.12*) The majority of adult patients who have malabsorption associated with a flat jejunal mucosa respond satisfactorily to treatment with a gluten-free diet. Some patients, however, respond poorly or not at all and in severe cases death may occur. It is generally considered that such patients may not have adhered strictly to a gluten-free diet. This paper, however, describes the clinical and pathological features of 10 patients who had malabsorption associated with a flat jejunal mucosa but who failed to respond to treatment with a strict gluten-free diet controlled in hospital. All 10 patients died.

Six patients (cases 1-6) had extensive abnormalities of the small intestinal mucosa at necropsy, with areas of ulceration, and in some cases, perforation; two of these patients (4 and 6) had widespread collagen deposition beneath the enterocytes, which in one case had not been present on biopsy a year earlier.

Two other patients (7 and 8) had widespread areas of ulceration with strictures of the small intestine; one patient (case 9) had tuberculosis which had not been suspected before necropsy. The final patient (case 10) first presented with signs of folic acid deficiency with only minor abnormalities of the jejunal mucosa on repeated biopsy. Although continuously treated for over a year with gluten-free diet and subsequently with Prednisone, the jejunal mucosa became flat and the patient developed severe malabsorption. At necropsy two years later there were widespread abnormalities of the small intestine despite adherence to a strict gluten-free diet.

These observations show that a flat jejunal mucosa on biopsy, found without evidence of concomitant disease, is not exclusively due to coeliac disease. The cause of malabsorption in such cases remains uncertain but the prognosis appears poor.

Autoantibodies to Reticulin in Patients with Various Gastrointestinal Diseases and their Relationship to Immunoglobulins and Dietary Antibodies

R. WRIGHT AND M. H. ALP (*Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford*) A variety of immunological disturbances has been reported in patients with coeliac disease. These include high-titre dietary antibodies (Taylor *et al*, 1961) as well as antibodies to reticulin (Seah *et al*, 1971) and basement membrane (Ammann and Hong, 1971) with or without immunoglobulin disturbances. Sera from over 600 patients with various forms of gastrointestinal disease and controls were examined for antibodies to reticulin and basement membrane using indirect immunofluorescence. Thirty per cent of 71 patients with idiopathic steatorrhoea, 44% of 75 patients with coeliac disease, 23% of 59 patients with Crohn's disease, 14% of 38 patients with aphthous ulceration, and 11% of 106 patients with ulcerative colitis had antibodies to reticulin and/or basement membrane, whereas the number of positives in patients with other forms of steatorrhoea and control subjects was negligible. A positive correlation between high-titre antibodies to dietary proteins and antibodies to reticulin or basement membrane was observed in the patients with coeliac disease and idiopathic steatorrhoea, whereas this was not noted in Crohn's disease. The relationship of these antibodies to specific immunoglobulin levels will be described as will the variation which occurred when serial observations were made

in patients with coeliac disease in response to a gluten free diet or gluten challenge. The value of these immunological changes in diagnosis and their possible role in pathogenesis will be discussed.

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Studies of Cellular Immunity of Liver Disease

P. A. BACON, H. W. BERRY, AND R. BOWN (introduced by A. M. Dawson) (*Departments of Experimental Pathology and Gastroenterology, St. Batholomew's Hospital, London*) There is extensive evidence for altered immunological reactivity in various forms of liver diseases with the demonstration of organ specific and non-specific autoantibodies, particularly in primary biliary cirrhosis (PBC) and chronic active hepatitis (CAH), but cell-mediated immunity (CMI) has been little investigated so far.

We have studied a series of such patients using the leucocyte migration test (LMT) as an *in vitro* test of CMI using two antigens. One was extracted by sonication and freeze drying from fresh adult cadaver liver. The other was extracted from adult salivary (parotid) gland and was chosen because of the known association of the Sicca syndrome with liver disease.

Eleven of 15 patients with PBC and eight of 11 with CAH showed significant reactivity to a dose of liver antigen which produced no reaction in 10 healthy people or 20 diseased patients without liver involvement and only weak reactivity in two of 17 patients with other liver disease. In a few patients this has been further validated using the lymphocyte transformation reaction to the liver antigens and also to a mitochondrial preparation derived from fresh foetal liver. There was no correlation between the CMI tests and the presence of circulating antimitochondrial antibody. A response to parotid antigen was seen in five of 15 patients with PBC and three of 11 with CAH but in none of the controls.

These results have been related to the clinical status of the patients and the presence of the Sicca syndrome.

Incidence and Pathogenesis of Multisystem Involvement in Chronic Liver Disease

P. L. GOLDING, M. G. M. SMITH, C. G. MITCHELL, A. KEMP, AND ROGER WILLIAMS (*From The Liver Unit, King's College Hospital, London, S.E.5*) Two hundred and twenty-eight patients with active chronic hepatitis, primary biliary cirrhosis, and cryptogenic cirrhosis were studied for evidence of multisystem involvement. Sjögren's syndrome and renal tubular acidosis were found most frequently—35% and 32% respectively but skin disorders (15%), arthropathy (14%), thyroid disease (8%), and neuropathy (5%) were also detected. There was no correlation with changes in circulating immunoglobulins nor with the presence of serum autoantibodies, but histological examination of the involved organs showed lymphocytic infiltration consistent with a cell-mediated immune response. Supporting evidence was obtained using the leucocyte migration test, a known measure of cell-mediated immunity. Abnormal responses to liver antigens were shown in 53% of the patients and to antigens from kidney and salivary gland in 40% and 59% of those with Sjögren's syndrome and renal tubular acidosis respectively. In contrast, none of the 65 patients with alcoholic cirrhosis gave abnormal results and in this group, apart from neuropathy (9%), evidence of multisystem involvement was not found.

To account for these findings it is suggested that hepatic damage from viral, drug, or toxic agents initiates a cell-mediated hypersensitivity which is responsible both for the perpetuation of the liver disease and, because of common surface antigens, for the other organ involvement.

Immunoglobulins, Virus-like Particles and Autoantibodies in Bile

M. H. ALP AND R. WRIGHT (*Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford*) The possibility that there may be selective excretion of immunoglobulins, virus-like particles, and autoantibodies in bile in various forms of liver disease has been examined. Duodenal juice and bile was collected from 30 patients with liver disease and healthy control subjects by duodenal intubation and stimulation with intravenous cholecystokinin. Unconcentrated bile and duodenal juice was tested for immunoglobulins by electro-immunodiffusion and for a variety of autoantibodies. After preliminary concentration bile was examined for Australia (Au) antigen and other virus-like particles by immunoelectro-osmophoresis (IEOP) and electron microscopy. Australia antigen or other virus-like particles were detected in bile by IEOP or electron microscopy in some patients. In addition the possibility that antigens present in bile might specifically stimulate lymphocyte transformation in patients with chronic liver disease has been examined. It has been shown that a factor present in bile from some patients

specifically stimulates lymphocyte transformation as judged morphologically and by the incorporation of H^3 thymidine. The results of tests for immunoglobulins and autoantibodies will be presented and their significance discussed.

Bacterial Agglutination by Secretory IgA from Human Gastrointestinal Secretions and Colostrum

D. B. L. MCCLELLAND, R. R. SAMSON, D. M. PARKIN, AND D. J. C. SHEARMAN (*Gastrointestinal Section of the University Department of Therapeutics, Royal Infirmary, Edinburgh*) IgA is the predominant immunoglobulin secreted into the gastrointestinal tract. Studies of its function have included an examination of the antibody responses in intestinal secretion and serum to polio vaccine (Ogra *et al*, 1968; Beale *et al*, 1971). The present study describes the *in vitro* assessment of upper gastrointestinal IgA function by its ability to agglutinate bacteria.

In initial studies, pure secretory IgA was prepared from pooled human colostrum by DEAE chromatography and gel filtration on Sephadex G. 200 (Newcombe *et al*, 1968). In concentrations between 1 and 50 mg% this IgA was shown to agglutinate, *in vitro*, a panel of enteric organisms. Prior incubation of IgA with acid plus pepsin, which resulted in an alteration of the IgA molecule as assessed by immunoelectrophoresis, prevented agglutination, but the IgA remained active after prior incubation with trypsin.

Secretory IgA was prepared from human gastric and jejunal secretions and tested by the above methods. In physiological concentrations it agglutinated some of the enteric bacteria. The IgA isolated from different patients showed variations in the enteric organisms agglutinated, but for the same individual, preliminary studies suggest that the same pattern of agglutination is seen for both gastric and intestinal IgA.

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Labelled Colonic Carcinoma Antigens[1]

M. D. TURNER, M. S. KLEINMAN AND W. THAYER (*Gordon Gastrointestinal Research Laboratory, University of Rochester, N.Y., and Division of Gastroenterology, Brown University, Providence, R.I.*) Extracts of human colonic carcinomata and absorbed antisera were prepared as before.[2] After ^{125}I labelling, the antigenic material appeared homogeneous on gel filtration, electrophoresis, and electrofocusing but showed three components on ultracentrifugation in CsCl. Two of these reacted with antisera prepared here and by Gold in Montreal, and contained group A determinants, though the antisera prepared here reacted with different determinants on the molecule. A sensitive radioimmunoassay developed with one component was used to examine sera from normals and from patients with a variety of diseases. Normal sera produced inhibition equivalent to not more than 5 ng antigen/ml. Seventeen of 21 sera from colonic carcinoma patients showed more than 5 ng/ml; the antigens levels were compared with the stage of the disease. Sera from a few patients with cirrhosis, Crohn's disease, and ulcerative proctitis showed more than 5 ng/ml though the majority fell in the normal range.

[1]Supported by grants CA-09546 and 5-TO-1-AM-05177 from USPHS.

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Fasting Plasma Gastrin Levels in Man

J. ARDILL, K. D. BUCHANAN, AND T. L. KENNEDY (*Department of Medicine, The Queen's University of Belfast and Department of Surgery, Royal Victoria Hospital, Belfast*) A radioimmunoassay for plasma gastrin has been established which has a sensitivity of between 30 and 100 pg/ml. Synthetic human gastrin (ICI) has been used for standards, iodinated hormone, and for antibody production. Similar dilution slopes of plasma samples with standards suggest immunological identity with human gastrin. Cross-reaction with cholecystokinin pancreozymin is low (6,000 times less on a molar basis) but none is noted with other pancreatic and intestinal hormones. Normal fasting plasma gastrin levels range from 0 to 200 pg/ml; and were not different in subjects with gastric ulcer and duodenal ulcer, except in two subjects suspected of suffering from the Zollinger-Ellison syndrome when elevated levels of 425 and 600 pg/ml were recorded respectively. Elevated levels of 786 ± 300 pg/ml (mean ± 1 SD) were recorded in Addisonian pernicious anaemia and could be suppressed by administration of acid. Normal levels have been recorded in two subjects with the WDHA syndrome and in one subject with a malignant insulinoma. Two patients with phaeochromocytoma had elevated levels (450 and 400 pg/ml). One of these patients was extensively studied and found to have severe hypochlorhydria which was reversed after removal of the tumour. The elevated gastrin levels could be suppressed by alpha-blockade and returned to normal following surgery.

Effect of Insulin Hypoglycaemia on Plasma Gastrin Concentration and Gastric Acid Secretion in Normal Subjects

P. C. GANGULI AND J. B. ELDER (*M.R.C. Clinical Endocrinology Research Unit, Edinburgh, and Gastrointestinal Centre, Southern General Hospital, Glasgow*)
Venous plasma gastrin concentration was measured by the radioimmunoassay of Ganguli and Hunter (1970) in the fasting state and at 15-minute intervals for two hours following injection of soluble insulin, 0·2 units/kg, in 13 informed healthy male volunteers. Gastric acid output after insulin was studied in 11. Blood sugar concentration fell to < 40 mg% in all subjects.

The mean increase in plasma gastrin concentration, 71%, was statistically significant ($P < 0.01$). Peak plasma gastrin concentration occurred at 30-45 minutes after the insulin injection in seven subjects, at 60-90 minutes in three, and no significant alteration from basal levels was noted in the three remaining subjects. Acid secretion was stimulated in all 11 subjects studied, while an increase in plasma gastrin concentration was noted only in nine of these 11. There was a significant negative correlation between total two hour post-insulin acid output and peak plasma gastrin concentration ($P < 0.05$).

The results suggest that insulin-induced vagal stimulation causes an increase in plasma gastrin level to a peak which is inversely proportional to the acid response.

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Glucagon and the Gut

K. D. BUCHANAN, R. ZANDOMENEGHI, R. F. MURPHY, AND J. D. TEALE (introduced by T. L. Kennedy) (*Department of Medicine, The Queen's University of Belfast*) A radioimmunoassay employing antibodies to pancreatic glucagon can be used to detect glucagon-like immunoreactivity (GLI) in the intestinal tract. Intestinal GLI in the pig is found in highest amounts in the jejunum, ileum and colon but sufficient amounts have not been purified to permit biological and chemical characterisation. However other studies suggest that there are important differences between intestinal GLI and pancreatic glucagon. Ninety per cent of intestinal GLI has a molecular weight greater than pancreatic glucagon, and occasional glucagon antibodies discriminate between the two materials. Previous work[1] has shown that intrajejunal glucose releases intestinal GLI but not pancreatic glucagon. Incubated pieces of rat small intestine show a striking linear release of GLI with concentrations of glucose between 5 and 40 g/100 ml; whereas pancreatic glucagon release from isolated pancreatic islets of the rat is stimulated by low glucose concentrations (30 mg/100 ml) and suppressed by concentrations of 300 mg/100 ml. Galactose has a small effect on intestinal GLI release but passively absorbed sugars such as mannose have no effect. In the clinical situation large amounts of intestinal GLI consistently appear in the circulation after oral glucose in patients with 'dumping' syndrome, whereas inconsistent small rises are noted in normal subjects.

Reference

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A Sensitive Method for the Biological Assay of Secretin

T. SCRATCHERD (*Teaching and Research Centre, University of Edinburgh, Western General Hospital, Edinburgh*) A sufficiently sensitive yet simple method for the assay of secretin in blood is highly desirable. A preparation which can detect secretin in biological fluids at concentrations in nanogram and upper picogram range of pure hormone can be devised using the isolated saline perfused pancreas as described by Case, Harper, and Scratcherd (1968.) By this method 2-10 ng of secretin can be detected regularly. However, it is possible to increase the sensitivity by a number of manoeuvres.

Secretin exerts its effects on the pancreas by stimulating adenyl cyclase to increase the concentration of cyclic AMP in the gland (Johnson, Sherratt, Case, and Scratcherd, 1970) By inhibiting phosphodiesterase, the enzyme which hydrolyses cyclic AMP, the response of the pancreas to secretin can be augmented by a factor of up to 10 or more. Other methods of increasing the sensitivity of the gland may be employed such as increasing the potassium concentration or lowering the osmolality of the perfusate.

Secretin when injected directly into the pancreatic arterial supply is not completely inactivated in a single passage through the gland and so recycling the perfusate will increase the response to a given dose of hormone. However, before reliable results can be obtained several precautions must be observed.

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Pancreozymin and Secretin in the Control of Pancreatic Exocrine Secretion

M. DOUGLAS AND H. L. DUTHIE (*University Department of Surgery, Royal Infirmary, Sheffield*) Recently it has been suggested that the actions of gastrointestinal hormones can be explained by common and linked receptor sites on the target organs (Grossman, 1970).

With the pancreas it is established that pancreozymin potentiates the action of secretin in stimulating bicarbonate secretion. The suggested theory holds that pancreozymin alone should influence bicarbonate output and secretin alone effect the enzyme output. There is little evidence to support these latter contentions.

This study investigates the influence of (1) secretin on enzyme secretion, (2) pancreozymin on bicarbonate output, (3) combinations of both hormones on the output of bicarbonate and enzymes.

Experiments were performed on six conscious dogs with established pancreatic and gastric fistulae. Secretin 0·25, 2·5, and 15·0 units/kg hr and pancreozymin 2·5 and 15·0 units/kg hr were used singly and in combinations on different occasions. Pancreatic juice was measured and assayed for bicarbonate and total proteins.

(1) Secretin had no effect on protein output. (2) Pancreozymin slightly increased the output of bicarbonate. (3) Pancreozymin greatly enhanced the bicarbonate output produced by a small dose of secretin but had less effect on the larger doses as the maximum output was approached.

Secretin did not influence pancreozymin stimulated protein output.

These results are only partially in agreement with the common receptor theory.

Reference

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Amylase Secretion and Calcium Efflux from Isolated Rat Pancreas

R. M. CASE AND T. CLAUSEN (*Institute of Physiology, Århus University, 8000 Århus C, Denmark*) Ca^{++} ions apparently act as an important signal in many secretory cells, but little is known of their role in pancreatic secretion. We have therefore studied the link between amylase secretion and ^{45}Ca efflux in this gland.

The thin, uncinate pancreas from 60-70g rats was loaded for 1 hr in Krebs-Ringer bicarbonate buffer containing ^{45}Ca. It was then transferred through a a series of vials containing normal buffer which was later analysed for ^{45}Ca and amylase. The fraction of ^{45}Ca lost/min became constant after one hour; amylase secretion was effectively constant throughout.

Cholecystokinin-pancreozymin and acetylcholine both accelerated ^{45}Ca efflux and amylase secretion within two min of addition, in a dose-dependent fashion. The accelerated ^{45}Ca efflux was probably not caused by general depolarization of the acinar cells since ^{42}K efflux was unaffected. Secretin was without effect on ^{45}Ca efflux but at high concentration did increase amylase secretion.

In Ca-free bathing media (containing 0·5 mM EGTA) basal amylase secretion was reduced; secretion stimulated by cholecystokinin-pancreozymin or acetylcholine was abolished but the accelerated ^{45}Ca efflux persisted.

It is suggested that cholecystokinin-pancreozymin and acetylcholine release Ca^{++} from intracellular stores and that the raised intracellular concentration of Ca^{++} triggers enzyme secretion by a mechanism which also requires the presence of extracellular Ca^{++}.

Quantitative Analysis of the Ultrasonic Liver Scan

R. A. MOUNTFORD, A. E. A. READ, AND P. N. T. WELLS (*Department of Medicine, University of Bristol, and Department of Medical Physics, United Bristol Hospitals*) The ultrasonic 'A' scan reveals multiple echo-producing targets within hepatic tissue. The amplitude and pattern of the returning echoes has been used to determine the histological state of the organ. Thus, normal liver tissue is said to give rise to scattered, low-amplitude echoes, whereas in cirrhosis there are masses of high-amplitude echoes[2,3].

A wide range of appearances occurs amongst 'A' scans taken within a single organ. In this study, 30 scans were taken from each of 30 normal controls and 13 patients with cirrhosis and the data from each combined to give an estimate of mean echo amplitude. An estimate of the rate of attenuation of ultrasonic energy was made but there was no significant evidence of a difference between the groups, as had previously been suggested[1].

Detailed examination of the configuration of the echoes revealed little difference between normals and cirrhotics. Further, two-dimensional 'B' scans identical to those found in cirrhosis can be produced in normal people by increasing the sensitivity of the machine. Possibly the same targets undergo a physical change in cirrhosis so that they produce a

larger (but otherwise unchanged) echo. Indirect evidence suggests that these targets are the blood vessels and possibly large bile ducts, and not fibrous tissue.

The immediate clinical importance of these results is that it is now possible to differentiate quantitatively between the ultrasonic scans of normal and cirrhotic livers.

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Hepatic Structure and Function in Psoriasis before and after Treatment with Methotrexate

D. BARNARDO, J. ALMEYDA, H. BAKER, J. LANDELLS, AND G. LEVENE (*Departments of Gastroenterology, Dermatology, and Pathology, The London Hospital and St. John's Hospital for Diseases of the Skin, London*) There have been reports of hepatic fibrosis and even cirrhosis in patients receiving methotrexate.[1,2,3]

We assessed hepatic function and obtained biopsies from 59 psoriatic patients. Twenty had not received methotrexate at the time of study and this group has formed the basis of a prospective survey as most have now received the drug and are being re-biopsied at intervals. Thirty-nine had received methotrexate for three to 80 months before biopsy. The two groups were otherwise comparable in all ways. Bromsulphthalein (BSP) retention was increased in six out of the 20 untreated patients. In seven (35%) the hepatic biopsy was abnormal, three (15%) showing fibrosis (one patient was alcoholic) and none, cirrhosis. In the 39 methotrexate-treated patients BSP retention was increased in a similar proportion (14 of 39) but in 24 (60%) the biopsy was abnormal, 12 (30%) showing fibrosis (one alcoholic) and three cirrhosis (all alcoholic). The cumulative dose was greater in those with hepatic fibrosis or cirrhosis ($P < 0.05$). Fibrosis, cirrhosis, inflammatory infiltrate, and steatosis were commoner in patients receiving methotrexate orally daily.

We conclude that methotrexate given for psoriasis can induce hepatic fibrosis (although this may occasionally be present before treatment) but have no evidence that methotrexate without alcohol excess causes cirrhosis.

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The Production and Transport of Ammonia in the Human Colon

R. L. BOWN, G. E. SLADEN, M. L. CLARK, AND A. M. DAWSON (*Department of Gastroenterology, St. Bartholomew's Hospital, London*) Two aspects of ammonia production and transport in the colon were studied in four patients with colonic exclusion for hepatic encephalopathy. A perfusion technique was used which initially demonstrated comparable water and electrolyte absorption to that previously reported in the human colon (Levitan, Fordtran, Burrows, and Ingelfinger, 1962).

We have not confirmed the recent suggestion (Phillips, Wolpert, and Summerskill, 1970) that a mucosal urease acting on plasma urea may be an important source of ammonia, as output by the perfused colon did not alter when either the urea concentration of plasma or perfusate was increased.

The net absorption of ammonia from the lumen has been shown to be markedly dependent upon *p*H; for example, at 800 μg per 100 ml initial ammonia concentration there is a change from net absorption to net secretion with a fall in *p*H from 7·3 to 5·6, confirming the role of non-ionic diffusion. However, at higher concentration (8000 μg per 100 ml) appreciable absorption takes place at the lowest *p*H studied (*p*H 4·2) suggesting absorption as ammonium (NH_4^+). The use of ^{15}N labelled ammonia demonstrated that luminal *p*H mainly affected ammonia flux from lumen to plasma.

In patients treated with lactulose we have observed a fall in caecal *p*H to levels comparable to those which markedly inhibit ammonia absorption (Sladen and Bown personal observations).

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The Effect of Acute Biliary Obstruction on Hepatic Cholesterol Biosynthesis in the Cholesterol-fed Rat

D. S. HARRY, M. DINI, AND NEIL MCINTYRE (*Medical Unit, Royal Free Hospital, London*) Cholesterol feeding causes a marked suppression of hepatic cholesterol biosynthesis in the normal rat. Obstruction of the biliary tree causes a striking increase in synthesis. It has been claimed by Katterman and Creutzfeldt[1] that the effect of biliary obstruction is dominant and that feedback control by cholesterol

feeding is not operative following biliary obstruction in the rat.

We have studied the effect of bile duct ligation and sham operation on hepatic cholesterol biosynthesis in rats previously fed a diet containing added cholesterol or a control diet. Cholesterol biosynthesis was assessed in liver slices from these animals by measuring the incorporation of acetate-2-^{14}C into digitonin-precipitable sterols (DPS).

Biliary obstruction caused a striking rise in acetate incorporation in animals on the control diet. This was apparent 24 hours after surgery and the increase continued over the next 48 hours. Sham operated rats showed a similar rise at 24 hours but there was a rapid return to normal levels.

Following cholesterol feeding acetate incorporation into DPS was markedly inhibited. When the bile duct was ligated in cholesterol fed animals the subsequent rise in acetate incorporation into DPS was greater than in sham operated rats but the inhibiting effect of cholesterol feeding was clearly evident in both groups.

Reference

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Treatment and Prognosis in Diffuse Jejuno-Ileitis

C. H. J. SWAN AND W. T. COOKE (*Nutritional and Intestinal Unit, The General Hospital, Birmingham 4*) Eighteen patients with diffuse Crohn's disease of the small bowel have been followed for periods varying from one to 32 years, nine of them for more than 10 years. Thirteen had developed symptoms before the age of 20 years, being 20% of all patients seen with onset of Crohn's disease before that age and all developed local cicatrizing disease eventually. Oedema was a prominent feature and was frequently associated with diarrhoea and colic. When seen initially anaemia was almost universal, while low serum folate was present in eight out of nine. Iron deficiency was present in half the patients at onset while low serum vitamin B_{12} levels occurred in two of 11. Lowered serum albumin and elevated serum seromucoid were present 13 of 16 and eight of nine respectively. Steatorrhoea was present in 10 of 16, but vitamin B_{12} absorption was normal in eight of eight when first seen. The outcome of 10 patients treated with steroids was not significantly different from that of eight patients who had not received steroids with regard to definitive surgery, death, and present clinical state. Four patients have died one to 18 years after the onset of the disease. The role of surgery in diffuse small bowel involvement is considered. In conclusion the outcome of diffuse small bowel Crohn's disease followed for a mean of 12 years has been good, for supportive therapy, haematinic supplements, and encouragement led to a satisfactory outcome in most patients.

A Double-blind Trial of Azathioprine in Crohn's Disease

J. M. T. WILLOUGHBY, P. KUMAR, J. BECKETT, AND A. M. DAWSON (*Department of Gastroenterology, St. Bartholomew's Hospital, London*) Azathioprine has been claimed to be effective in the treatment of Crohn's disease, but controlled data have been few. The present double-blind trial was therefore undertaken with the particular object of assessing the value of azathioprine in maintaining remission of Crohn's disease induced by corticosteroid therapy.

Of 19 patients studied, 10 were admitted in acute relapse or a first attack and nine were outpatients who needed 7·5-15·0 mg prednisolone daily to maintain good health. The latter were prescribed azathioprine at 2 mg/kg/day (or placebo) in addition to their usual prednisolone, and the former initially a double dose of azathioprine or placebo together with prednisolone 60 mg daily, both drugs being reduced early to dosages comparable with those used in the other group. Thereafter prednisolone was gradually discontinued in all patients under uniform conditions.

Nine of 10 patients taking azathioprine completed the 24-week period in acceptable health, whereas six of nine on placebo relapsed and were withdrawn early. While patients on azathioprine spent a mean 10·6 weeks off prednisolone, the corresponding figure for those taking placebo was 4·2 weeks. These differences, which are significant at the 5% level within each group, suggest that azathioprine is effective in holding a remission of Crohn's disease.

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Crohn's Disease of the Mouth and Lips

K. F. R. SCHILLER, P. L. GOLDING, R. A. PEEBLES, AND R. WHITEHEAD (*Departments of Medicine, St. Peter's Hospital, Chertsey, and King's College Hospital, London, Department of Facio-Maxillary Surgery, St. Peter's Hospital, Chertsey, and Department of Pathology, Radcliffe Infirmary, Oxford*) Three patients with oral and one with labial Crohn's disease are described. The first patient, a boy of 11, presented with a perianal abscess, which was drained. Fragments of the abscess wall showed changes compatible with Crohn's disease. He was

lost to follow up until 1970 when he was referred for investigation of an hypertrophic oral mucosa. Examination revealed, in addition, an asymptomatic perianal fistula. Biopsy appearances from both sites suggested Crohn's disease. Other relevant investigations were negative. The second patient, a woman, had diarrhoea since the age of 25. At 40 she had a right hemicolectomy, and at 53 a massive small bowel resection, both for Crohn's disease, since when she has had no bowel symptoms. At 54, three years ago, she developed a tender swelling at the left lower gingival margin and an indurated polypoid lesion inside the right cheek. Biopsies from both areas showed changes compatible with Crohn's disease. The lesions did not regress on systemic steroid treatment. The third patient developed a linear ulcer in the right lower buccal sulcus at 17. Subsequently he had two partial small bowel resections for Crohn's disease. In 1969, at 28, he still had the original mouth ulcer in an area of ridging, and similar ridging in both upper buccal sulci. Local steroid treatment cleared the ulcer and the ridged lesions after a period of several months. The fourth patient presented in 1968 at 25 with scleritis and an ESR of 57 mm/hr, followed a few months later by weight loss, diarrhoea, and erythema nodosum. Barium studies showed the appearances of Crohn's disease in the terminal ileum and the transverse colon. Two and a half years later while on systemic steroid treatment he developed a painful fissure in a very swollen lower lip. The fissure was excised and changes of Crohn's disease were seen in the sections. Only two reports of oral Crohn's disease appear in the literature (Dudeney and Todd, 1969; Issa, 1971). It would seem that the oral and labial manifestations of Crohn's disease may appear in either sex at any age, are not related to the severity of extent of the alimentary disease, and may be resistant to treatment.

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The Anal Lesion as the Sole Presenting Symptom of Intestinal Crohn's Disease

W. N. W. BAKER AND G. J. MILTON-THOMPSON (introduced by H. E. Lockhart-Mummery) (*Research Department, St. Mark's Hospital, London, EC1*) In a review of 262 patients undergoing treatment for Crohn's disease at St. Mark's Hospital between 1950 and 1969 it was found that 215 (82%) had anal lesions, and that in 61 (24%) the development of the anal lesion preceded the onset of intestinal symptoms by a mean of four years (range of one month to 22 years). There were 38 men and 23 women in this group in contrast to an overall sex ratio of 1:1.

The presenting anal lesions encountered were oedematous skin tags (5 patients), fissures (18 patients), abscesses (21 patients), and fistulae (24 patients). Twelve patients had more than one presenting lesion. Forty-two of those patients with an anal lesion as the presenting symptom subsequently developed symptoms of intestinal disease within five years of the onset of the anal lesion. Eleven patients developed disease in the ileum only, 12 developed ileo-colic disease, and 30 developed disease confined to the large bowel. Eight patients with anal lesions histologically positive for Crohn's disease have had no intestinal symptoms so far, but as the mean follow up time is only five years, it is possible that most will do so in time.

The Effect of Vagotomy Upon Pepsin I Secretion in Man and its Possible Role in Duodenal Ulceration

C. W. VENABLES (*Department of Surgery, University of Newcastle upon Tyne*) In earlier studies (Venables, 1969) it has been shown that 'activity' in duodenal ulceration is associated with an increase in peptic activity at all levels of acid secretion. Peptic activity is a measure of the total proteolytic activity of a number of isoenzymes of pepsin and it is possible that this increase might be due to alterations in the secretion of one of these. The present study was planned to investigate the role of pepsin I (gastricsin) in duodenal ulceration and the effect of vagotomy upon it.

Seventy-two patients were investigated both before and six weeks after truncal vagotomy and pyloroplasty using a combined pentagastrin-insulin secretion study. Twenty-two of the patients were found to have 'inactive' ulcers at the time of operation.

Pepsin I was measured by a modification of the method described by Turner *et al* (1967) and outputs of acid, pepsin I, and total peptic activity were calculated for the hour after pentagastrin and the peak 30 minutes after insulin.

Before operation pepsin I secretion was significantly higher ($P < 0.01$) in the 'active' than 'non-active' group. Vagotomy resulted in a 77·3% reduction in the 'active' and 59·8% reduction in 'non-active' group in pepsin I secretion. This reduction was larger than that for either acid (59·8% in the 'active') or other peptic activity (45% in the 'active' group) in both groups. When pepsin I secretion was correlated with acid secretion the regression line obtained following vagotomy in the 'active' ulcer group was similar to that found in the 'non-active' group preoperatively.

These findings suggest that pepsin I secretion may have an important role in the 'activity' of duodenal ulceration and that the beneficial effects of vagotomy may be related to the changes in its secretion following this operation.

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Does Highly Selective Vagotomy Preserve Antral Motility?

J. M. KELLY AND T. L. KENNEDY (*Department of Surgery, Royal Victoria Hospital, Belfast*) In 'highly' selective vagotomy it is assumed that antral motility will be unimpaired, gastric emptying will be normal, and a drainage operation will be unnecessary (Amdrup and Griffiths, 1969; Johnston and Wilkinson, 1970).

This work was undertaken to test the validity of the hypothesis by observing antral motility before and after surgery using a miniaturized mercury column strain gauge, developed for long-term implantation on the serosal surface of the dog's stomach.

Both resting and seven-hour postprandial motility contours of the antrum have been recorded in six normal dogs. In the first 45 minutes after eating, antral motility is of moderate amplitude and accompanied by terminal antral contraction—retaining food in the stomach. Subsequently contractions become sequential, increase in vigour and sweep right down to the pylorus, expelling food from the stomach.

Motility recordings one month after truncal (2 dogs) and selective vagotomy (2 dogs, all Hollander negative) show that the normal pattern is replaced by the type of activity usually seen in the resting stomach (Hightower and Code, 1950).

After highly selective vagotomy (3 dogs, Hollander negative) motility is well maintained but the quality is altered. There is no terminal antral contraction; propulsive waves of high amplitude occur within five minutes of eating.

These results suggest that omission of drainage is safe with 'highly' selective, but not with selective or truncal vagotomy.

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Evidence for Partial Vagal Reinnervation of the Stomach after Highly Selective Vagotomy without a Drainage Procedure (HSV) For Duodenal Ulcer in Man

E. AMDRUP AND E. KRAGELUND (*University Department of Surgery, Arhus, and Surgical Department I, Kommunehospitalet, Copenhagen, Denmark*) AND C. S. HUMPHREY, R. B. SMITH, J. C. GOLIGHER, AND D. JOHNSTON (*University Department of Surgery, The General Infirmary, Leeds*) We reported previously to the Society encouraging early clinical results in 110 patients treated by HSV[1,2]. The early insulin tests (IT) were negative in 97%. This paper analyses the results of 55 ITs and 50 pentagastrin tests (PGTs) performed more than one year after HSV. The ITs were judged by multiple criteria.

Spontaneous acid output (SAO) was 5·8 ± 0·6 m-equiv/hr before HSV, 0·4 ± 0·1 at one week, 0·5 ± 0·1 at 3 months, 0·7 ± 0·2 at 9 months, and 1·0 ± 0·2 m-equiv/hr at 16 months after HSV, an 82% reduction. The increase in SAO between 3 and 16 months was significant ($P < 0.05$). Mean PAO in the PGTs in m-equiv/hr was 39·2 ± 2·5 before HSV, 18·6 ± 1·4 at one week, 12·1 ± 1·6 at 3 months, 17·8 ± 2·3 at 9 months, and 18·1 ± 2·1 at 16 months after HSV, a final mean reduction of 54%. The increase in PAO between three and 16 months was significant ($P < 0.01$).

Thirty-one of the 55 ITs performed more than one year after HSV were Hollander-positive. Seventeen were early-positive in the first hour after insulin. Mean PAOs in the ITs were 32·0 ± 2·0 before HSV, and 4·6 ± 0·7 m-equiv/hr more than one year after HSV. PAO-IT : the preoperative PAO-PGT was 72·4% before and 4·0%, 6·5% and 10·5%, three, nine, and 16 months after HSV. This increase in PAO-IT with time was significant ($P < 0.01$).

The significant increase in acid output during the first year after HSV is probably due to partial vagal reinnervation of the parietal cell mass. Its clinical significance is as yet uncertain.

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The Prevention of Post-vagotomy Diarrhoea

C. S. HUMPHREY, B. WALKER, C. N. PULVERTAFT, J. C. GOLIGHER, AND D. JOHNSTON (*The Gastric Follow-up Clinic and the University Department of Surgery, the General Infirmary, Leeds*) Diarrhoea after vagotomy presents a difficult therapeutic problem. Prevention would be the best solution. Although

bilateral selective vagotomy (SV) produces significantly less diarrhoea than does truncal vagotomy (TV)[1], diarrhoea is not abolished by this modification. Post-vagotomy diarrhoea may be partly attributable to the accompanying drainage procedure[2,3], and therefore highly selective vagotomy without a drainage procedure (HSV) might be expected to reduce still further the incidence of diarrhoea.

Bowel habit in three groups each of 50 consecutive patients one year after TV+P, SV+P, or HSV was assessed 'blind' in the Gastric Follow-Up Clinic. The incidence of diarrhoea was 20% after TV+P, 18% after SV+P, and 2% after HSV. Severe diarrhoea was found in 5% after TV+P, 2% after SV+P, and 0% after HSV. Five to eight years after TV+P in 160 patients the incidence of diarrhoea was 22% (severe in 4%) and two to five years after SV+P in 90 patients the incidence was 16% (severe in 1%), which suggests that the findings at one year are permanent.

Thus diarrhoea is virtually absent after HSV without a drainage procedure, and troublesome diarrhoea after surgery for duodenal ulcer may be abolished by the use of this technique.

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Studies in the Rates of Epithelial Cell Exfoliation from the Gastric Mucosa in Normal and in Ulcer Subjects

B. E. BOYES, G. P. CREAN AND G. WATKINSON (*Gastrointestinal Centre, Southern General Hospital, Glasgow, S.W.1*) The cell kinetics of the gastric mucosa have been shown to be deranged in patients with gastric ulcer, gastric neoplasm, and atrophic gastritis (Teir and Rasanen, 1961). The reproducibility of the method of assessing cell exfoliation (Croft, Pollock, and Coghill, 1966) has been confirmed and the method used to investigate rates of exfoliation in 30 normal subjects, 22 patients with duodenal ulcers, 38 patients with gastric ulcers, 15 with combined ulcers, and in 18 patients with gastric hyposecretion.

In patients with an intact gastric mucosa exfoliation was found to be greatest in patients with gastric hyposecretion and progressively slower in patients with duodenal ulcer, normal subjects, and patients with pernicious anaemia.

In gastric ulcer subjects it has been found that the size of the ulcer did not affect the exfoliation rates at the time of the initial study and that patients with healed ulcers had a lower mean rate of exfoliation. Serial studies during healing were made and the effect of ulcer site on exfoliation assessed.

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The Demonstration of Polypeptide Hormone-secreting Cells in the Gastrointestinal Tract

I. M. P. DAWSON (*Westminster Medical School, London*) Enterochromaffin (e.c.) cells secreting 5-hydroxytryptamine ('argentaffin' or Kulshitsky cells) are now becoming recognised as part of a larger family of APUD (amine precursor uptake and decarboxylation) cells which can decarboxylate arylethylamine precursors to yield biological amines and also secrete a number of different polypeptide hormones. A separation of some of the cell types within this family, which are found scattered through other endodermal derivatives besides the gut, is now possible using histochemical, fluorescent, immunofluorescent and electron microscopic techniques. In general, though freeze drying with subsequent aldehyde vapour fixation is the technique of choice for histochemistry, fixation using buffered glutaraldehyde allows electron microscopic investigation and is a satisfactory alternative for most histochemical procedures. Sections are examined for aldehyde-induced fluorescence, which allows some amine separation, for aldehyde-amine conjugates which have reducing and coupling properties, and for reactive side chains and terminal carboxyl groups of polypeptides. The value of different techniques and the suggested choice of procedures for particular problems is outlined.

Histopathology of Cathartic Colon

B. C. MORSON (*Pathology Department, St. Mark's Hospital, London*) It is well established that the ingestion of an excessive quantity of purgatives can lead to a diarrhoeal state with potassium deficiency, excessive loss of water, or protein-losing enteropathy.[1] The symptoms and barium enema appearances can mimic ulcerative colitis. Purgative addiction probably damages the myenteric plexus of the colon leading to a failure of gut motility which converts the colon into an inert tube.[2]

In this paper the histopathology of cathartic colon is described. Attention is focused on the value of rectal biopsy; in particular the significance of melanosis coli, the presence of mucosal inflammation, and other changes. In surgical specimens the mucosal abnormality is usually but not exclusively found in

the right colon and has been compared to the appearance of the skin of a toad's back. There is patchy but very pronounced thickening of the muscularis mucosae and an excessive quantity of adipose tissue in the submucosal layer. The muscularis propria is usually much thinner than normal. Melanosis coli always seems to be present in cathartic colon, but can also be found in patients who have not developed symptoms of this syndrome. It is concluded that the histopathology of cathartic colon is distinctive and can be distinguished from other muscular and inflammatory bowel disorders.

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Experimental Ulceration of the Colon Induced by Non-algal Sulphated Products

R. MARCUS AND J. WATT (introduced by R. B. McConnell) (*Clatterbridge Hospital, Bebington, and Department of Pathology, University of Liverpool*) The finding that carageenan, a sulphated polysaccharide derived from red seaweeds, causes ulcerative disease of the colon in several species of laboratory animals is important because of the widespread use of carrageenan as a food additive (Marcus and Watt, 1969). To determine whether this ulcerogenic property is confined to algal sulphated polysaccharides, we investigated two sulphated products not derived from seaweeds, namely sodium lignosulphonate and sulphated amylopectin. Sodium lignosulphonate, a biproduct from the spruce tree obtained during the manufacture of wood pulp, is a polymer consisting of sulphonated phenylpropane units. Sulphated amylopectin is a synthetic product derived from potato starch.

Aqueous solutions of these substances (0·1-1%) were supplied to laboratory animals as drinking fluid for periods of two to six weeks. Both substances caused ulceration of the colon in one or other of the two species (guinea-pig and rabbit) investigated, the incidence of ulceration ranging from 50 to 100%. These studies raise the possibility that human ulcerative colitis may be due to the presence in our food of sulphated polysaccharides or other substances which behave as polyanionic agents and which in small amounts may interfere with the protective mechanisms in the colon and lead to ulcerative disease.

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Scientific Subcommittee of the British Society of Gastroenterology. Study of Severity in Ulcerative Colitis; Interim Report

W. I. CARD As a first step towards a system of classification of ulcerative colitis, an attempt has been made to classify its severity. A group of members with special interest in ulcerative colitis agreed to collect prospective records containing certain agreed data. From these records, 25 were selected to show a range of severity from very severe to mild. This set of records has been examined independently by a number of consultants with experience of this disease who ranked the set in order of severity. The extent of agreement between the various consultants can then be measured and a ranking order based on their consensus judgement can then be calculated. It is then possible to see how closely the 'consensus order' can be simulated by weighting the individual characters from the case record and arriving at a score which measures the 'severity' of that patient. The results obtained will be described. The method has an application to any general problem of classification such as the allocation of a patient to a treatment class, where if for any reason no informative experiment is possible, we can only be guided by the group judgement of a body of experts.

Intravascular Coagulation in Acute Hepatic Necrosis: Clinical and Experimental Studies into the Deposition of Microthrombi and the Effect of Treatment

M. O. RAKE, P. T. FLUTE, K. B. SHILKIN, AND R. WILLIAMS (*From the Liver Unit, and Department of M.A. Haematology, King's College Hospital, London, S.E.5*) Bleeding is a major complication of acute hepatic necrosis and on the basis of an increased ^{125}I fibrinogen plasma disappearance together with thrombocytopenia it has been attributed to the development of disseminated intravascular coagulation in addition to the impairment of hepatic synthesis[1]. Subsequent experience showed that correction of these changes by heparin proved difficult once major bleeding had occurred. In three recent patients with hepatic coma due to acute hepatic necrosis we have used a combination of intensive and high dosage heparin therapy together with fresh frozen plasma starting immediately after admission. This was followed by striking improvement with return of the prothrombin time to normal over seven days. All three patients recovered completely. Liver biopsies taken during the recovery phase showed fibrin deposition within the hepatic sinusoids and the possible role of these microthrombi in the pathogenesis of the liver necrosis has been

investigated further in rats with hepatic necrosis induced by carbon tetrachloride. Similar haematological changes were demonstrated and a significant accumulation of ^{125}I fibrinogen was found in both liver and spleen but not in the lung, heart, or kidneys. That this liver accumulation was due to microthrombi was confirmed by light and electron microscopy. Although heparin administration slowed the disappearance rate of ^{125}I fibrinogen, total liver accumulation was unaltered and this is in accord with the clinical experience indicating that large doses of heparin are necessary to bring the coagulation disturbance under control.

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Further Observations on the Lundh Test Meal in the Diagnosis of Pancreatic Disease

S. L. WALLER, A. MOTTALEB, H. S. WIGGINS, T. D. KELLOCK, AND F. KAPP (*Medical Research Council Gastroenterology Unit and Department of Gastroenterology, Central Middlesex Hospital, London, NW10 7NT*) Bramwell Cook and his colleagues (1967) have shown that in a selected group of patients the measurement of the mean two hour tryptic activity (MTA) following the ingestion of the Lundh test meal was a useful index of exocrine pancreatic function[1]. As a result of their findings the Lundh test meal was continued as a routine diagnostic procedure in this Department.

The results of 360 routine studies performed on 344 patients during the past four and a half years have been analysed. It was found that of 119 patients with a proven diagnosis other than pancreatic disease less than 1% had a MTA below 6 IU whilst in 9% the MTA was between 6 and 10 IU. In marked contrast 31 of the 45 patients (69%) with proven chronic pancreatitis or pancreatic carcinoma had a MTA below 6 IU, in 15% the MTA lay between 6 and 10 IU whilst in only 15% was the MTA greater than 10 IU. These present findings confirmed the value of the Lundh test meal as a routine procedure in the differential diagnosis of steatorrhoea and jaundice.

The test was simple to perform, did not disturb the patient unduly, and could be repeated when necessary to follow the progression of pancreatic disease. In many instances additional information could be obtained from simple observation of the aspirate.

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Assessment of Drug-induced Gastric Bleeding

D. N. CROFT, J. H. P. CUDDIGAN, AND C. SWEETLAND (*St. Thomas' Hospital, London*) New formulations of aspirin are produced each year and some are claimed to cause less gastric bleeding. The current methods of assessing gastric bleeding are cumbersome as the patient has to collect stools for two weeks or more. The ^{51}Cr tagged red cell technique has been simplified in order to make it appropriate for the outpatient screening of new drugs. The patient has to attend hospital on only three occasions and collect eight stool specimens[1]. Using this method two new aspirin fomulations have been studied. Choline salicylate, which had previously been reported to cause no gastric bleeding[2], caused as much bleeding as soluble aspirin. Benorylate, a new esterified aspirin (4(acetamido) phenyl 2-acetoxybenzoate), caused insignificant bleeding in 13 of 15 subjects studied. In the benorylate trial 27% did not bleed with aspirin or benorylate, 69% bled small amounts with aspirin but did not bleed with benorylate, 14% bled with both aspirin and benorylate. The significance of variable aspirin-induced occult bleeding with regard to drug-induced haematemesis and melaena will be discussed in relation to one patient who bled 1·2 litres.

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Gastrointestinal Iron Losses in Atrophic Gastritis, Postgastrectomy States and Adult Coeliac Disease

D. R. SUTTON, I. MCL. BAIRD, J. S. STEWART, D. N. CROFT, AND N. F. COGHILL (*West Middlesex Hospital, Isleworth, Middlesex*) In many patients with atrophic gastritis, postgastrectomy states, and adult coeliac disease neither malabsorption of iron nor blood loss are sufficient to account for the presence of iron deficiency anaemia. Increased free radioiron loss from the gut has been demonstrated in these conditions[1]. The significance of this preliminary study has become apparent by further studies using a double isotope technique with ^{51}Cr and ^{52}Fe, and these estimations validated by comparing the isotopic results with biochemical analysis. Free iron losses have also been related to gastric cell turnover rates.

No evidence of excessive blood loss was found in the majority of patients either using ^{51}Cr or by long term ^{52}Fe loss studies using a whole body counter. In most patients with atrophic gastritis, postgastrec-

tomy states, and adult coeliac disease a mean daily increase of between 0·4 and 1·6 mg of free iron was detected. This, in the presence of iron malabsorption, which was also found, may be an important factor causing iron deficiency. Free iron is probably lost with desquamated mucosal epithelial cells, since in the presence of increased cell turnover the free iron loss was usually also increased.

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