41. THE HISTAMINE CONTENT OF HUMAN GASTRIC JUICE AFTER PENTAGASTRIN AND INSULIN STIMULATION

CHRISTINE BRUCE and W. H. TAYLOR

Department of Chemical Pathology, Liverpool Area Health Authority (Teaching), Liverpool

The quantity of histamine entering gastric juice has been followed during standard intramuscular pentagastrin tests in 10 patients (six duodenal ulcer, one gastric ulcer and three non-ulcer dyspepsia), and during standard insulin tests in three (all duodenal ulcer).

Following pentagastrin, peak histamine output occurred from 0-5 to 30 min in six patients and from 15-30 min in two. All output peaks followed the histamine peaks by 15 min in four patients, by 30 min in two and by 45 min in one; in one patient the peaks coincided at 15-30 min. In two patients acid output peaks were not preceded by increases of histamine output.

Following insulin, acid output peaks occurred at 45-60 min in one patient and at 75 to 90 min in two. In all three patients acid secretion occurred without a significant preceding increase of histamine output.

Overall, the results show that, after pentagastrin, histamine is released into gastric juice and the release precedes the peak acid output. After insulin there is no such release. The results are compatible with the hypothesis that pentagastrin acts via histamine in stimulating acid secretion.

42. PLASMA TRYPsin IN PATIENTS WITH STEATORRHOEA DUE TO CHRONIC PANCREATITIS

T. E. ADRIAN, H. S. BESTERMAN, C. N. MALLINSON, C. GALAROTIS and S. R. BLOOM

Department of Medicine, Royal Postgraduate Medical School, London and V G I Unit, Greenwich District Hospital, London

Trypsin is a pancreatic endopeptidase secreted into the duodenum in response to food. In addition trypsin enters the duodenum in response to food. In addition trypsin enters the duodenum in response to food.

After insulin there is no such release. The results are compatible with the hypothesis that pentagastrin acts via histamine in stimulating acid secretion.

43. A NEW METHOD FOR STUDYING EPITHELIAL PERMEABILITY CHARACTERISTICS IN VIVO

C. J. EDMONDS and T. SMITH

Division of Radios isotopes, Clinical Research Centre, Harrow, Middlesex

Unidirectional flux rates and net transport rates of polar and non-polar molecules have been widely studied by tracer techniques in a variety of epithelia under various conditions. These experiments treat the epithelium itself as a 'black box', the measurements being made when epithelial conditions are supposed in a steady state. Studies during the initial transient phase can, however, give considerable information about the way molecules move through the epithelium. The present method was designed to exploit this possibility and will be described in application to colonic epithelium of the rat.

A bolus injection of a chosen mixture of radios isotopes is given intravenously to an anaesthetized animal in which a loop of intestine has been previously cannulated. The cannulated segment is rinsed continuously during the experiment and the effluent collected so that the rate of secretion of the tracers can be continuously recorded. Frequent blood sampling through an indwelling venous cannula enables the changes of blood levels of the tracers to be recorded. By computer-assisted deconvolution analysis of the data, a function representing the output of the epithelium on the mucosal side in response to a known delta input on the serosal (blood) side can be obtained for each tracer. The method is free of any assumption such as are used in compartmental analysis. Thus functions reflecting the kinetics of epithelial transfer of chosen molecules are obtained and can be compared with each other and with the behaviour of defined models. The effects of modifications in epithelial function on the movement of molecules through the tissue such as may be induced by drugs and hormones can be examined. The results obtained using a mixture of 32Na, 45Ca and 36Cl will be discussed.

44. MITOCHONDRIAL IRON UPTAKE AND SUBCELLULAR DISTRIBUTION OF IRON IN GUINEA PIG SMALL INTESTINE

J. M. P. HOPKINS, T. M. COX and T. J. PEETERS

Department of Medicine, Royal Postgraduate Medical School, London

The mechanism and control of iron absorption is poorly understood. It has been suggested that mitochondria may play a regulatory role at a mucosal level (Worwood & Jacobs, 1975, British Journal of Haematology, 22, 265). The uptake of radiolabelled iron by enterocytes was investigated by application of analytical centrifugation techniques to determine the subcellular distribution of iron.

FeCl3 (90 nmol) in 0-15 mol/l NaCl-5 mmol/l HCl (containing 5 μCi of labelled iron) was injected into 15 cm closed jejunal loops of anaesthetized guinea pigs. The contents of the loops were washed out and the enterocytes isolated, homogenized and fractionated by either differential or zonal centrifugation, at various intervals. After 5 min the subcellular distribution of radioiron in each fraction after differential centrifugation was as follows: nuclear 27%, mitochondrial 46%, microsomal 13% and soluble 14%. Mitochondrial iron uptake was conclusively demonstrated by complete separation of contaminating organelles from the mitochondria by rate zonal centrifugation (Peters & Shio, 1976, Clinical Science and Molecular Medicine, 50, 353). Subfractionation of the mitochondria after sonication or digitonin treatment showed that the radioiron was associated with both inner membrane and matrix components indicating an energy-dependent uptake of iron by this organelle (Romslo & Fallmark, 1974, Biochimica et Biophysica Acta, 347, 160). Chromatographic analysis (Drysdale & Ramsay, 1965, Biochemical Journal, 95, 282) of the mitochondrial fractions indicated...
that the labelled iron was mainly (85%) associated with the transferrin fraction. These experiments demonstrate a very rapid uptake of iron into the erythrocyte mitochondria suggesting that it plays a regulatory role in controlling absorption.

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45. MONOCYTE ACTIVITY IN CROHN'S DISEASE AND ULCERATIVE COLITIS

A. S. MEE and D. P. JEWELL

Department of Medicine, Royal Free Hospital, London

Macrophages present in granulomata are derived from circulating blood monocytes. The activity of monocytes has therefore been investigated in patients with Crohn's disease (CD) and ulcerative colitis (UC).

Absolute monocyte counts in peripheral blood smears were estimated by staining for non-specific esterase. Activity of a specific lysosomal enzyme N-acetyl-β-D-glucosaminidase was measured in blood monocytes, isolated over a Ficoll-Triosil gradient, using a fluorimetric method.

Monocyte counts were determined in 30 patients with UC, 27 patients with CD and 36 normals. The mean counts (±SEM) were 770 ± 84 (UC), 652 ± 65 (CD) and 540 ± 39 (normals). Patients with UC have significantly higher counts than normal controls (P = < 0.0005). This increase was associated with disease activity (P = < 0.0005).

Mean lysosomal enzyme activity was 3.51 nmol h−1 10−4 cells (normals), 3.02 nmol h−1 10−4 cells (CD, P = < 0.00025) and 2.74 nmol h−1 10−4 cells (UC, P = < 0.0005). Active disease was associated with higher enzyme levels.

Serial studies in individual patients treated with Prednisolone showed that the level fell as the disease remitted. Corticosteroid therapy had little effect on enzyme levels in eight normal volunteers given 20 mg of prednisolone daily for 1 week.

The evidence suggests that monocytes are activated in inflammatory bowel disease and that this appears to be related to disease activity.

46. A METHOD OF FORMAL ASSESSMENT AND RATIONAL INTERPRETATION OF CLINICAL EVIDENCE IN THE DIAGNOSIS OF ACUTE ABDOMINAL PAIN

D. E. H. LLEWELYN, D. INGRAM, JANE C. HOBROCKS and F. T. DE DOMBAL

Professors of Medicine, St Bartholomew's Hospital, London and Department of Surgery, St James' Hospital, Leeds

The formal assessment of therapeutic regimens has been well established for many years, and recently there has been an increasing interest shown in the study of the diagnostic process itself (Journal of the Royal College of Physicians, London, 1975, 9, no. 3). An improved understanding of the latter would allow a more rational assessment and comparison of investigative methods in clinical medicine.

A mathematical representation of diagnosis by a process of elimination in terms of probabilities has already been described (Llewelyn, 1975, Clinical Science and Molecular Medicine, 49, 69–78) and this, when combined with the use of some diagnostic symptoms and signs, has now been applied to a data base and test cases collected from patients admitted to a surgical unit with acute abdominal pain (de Dombal et al., 1972, British Medical Journal, 11, 9–13). The approach of inference by elimination and use of diagnostic pieces of evidence provided a 'correct' diagnosis in 85 out of 100 cases, compared to 81 out of 100 cases using the Bayesian relative likelihood method, and 80 out of 100 by an experienced surgeon.

An example of the 'rational' approach is provided by the following: 'Given the presence of right iliac fossa pain, the patient probably (P ≥ 0.96) has appendicitis or non-specific abdominal pain. Guarding is also present, and as the latter is part of a classical presentation of appendicitis but rarely (9/100) found in non-specific abdominal pain, the latter is unlikely (P ≤ 0.29), the probable diagnosis being appendicitis (P ≥ 0.67). However, if guarding had been absent, as this usually (83/100) occurs in appendicitis, the latter would be unlikely and the diagnosis probably (P ≥ 0.52) non-specific abdominal pain.' The classical presentation of appendicitis used in this context was admission to the (Leeds) department of surgery, with acute abdominal pain in the right iliac fossa, accompanied by rebound tenderness and guarding. All this occurred in 54/100 cases of appendicitis in the data base.) The components of the classical presentation were selected because they discriminated against some of the differential diagnoses considered (non-specific abdominal pain, cholecystitis, perforated duodenal ulcer, small bowel obstruction, diverticulitis and pancreatitis), and when taken in certain combinations in the 'logical' manner indicated above, discriminated against all others. Murphy's sign was an example of those used as diagnostic pieces of evidence as presented with this sign in the data base usually (P = 0.90) had cholecystitis.

A series of computer programmes were written to examine the discriminating power of the recorded evidence (taking relative incidence of the diagnostic categories into account) and assembling the classical presentations. Another programme was written to execute the process of elimination outlined above, and also calculated the various probabilities and probability limits produced by this approach.

This study illustrates the possibility of formally assessing the quality of clinical evidence and then selecting a small fraction (12 clinical questions and 18 answers from an original 35 questions and 131 possible answers in terms of present or absent symptoms and signs) as being particularly useful. It also seems possible for this limited information to be used in a rational manner without necessarily using a computer, and in this case resulting in a performance which is essentially the same as standard computer-aided methods and also an experienced clinician in the field.

47. α2-MACROGLOBULIN IN INFLAMMATORY BOWEL DISEASE

D. P. JEWELL, D. BROWN, J. KHAN and G. P. COPELAND

Department of Medicine, Royal Free Hospital, London

α2-Macroglobulin (α2-M) inhibits serine proteases including trypsin, coagulating factors and complement components. Patients with ulcerative colitis (UC) and Crohn's disease (CD) have been investigated to determine serum levels of α2-M, using radial immunodiffusion. Immunofluorescent techniques were used to quantify α2-M-bearing and immunoglobulin-bearing mononuclear cells in peripheral blood.

Mean levels of α2-M were: UC, 2.25 g/l (n = 61); CD, 2.16 g/l (n = 41) and in healthy controls 2.48 g/l (n = 47). The mean value for CD was significantly lower than the mean for the controls (P < 0.03). For both disease groups, α2-M was significantly lower during a relapse.

The mean proportion of mononuclear cells bearing α2-M was 4.9% in control subjects (range 3–12%, n = 17). Similar results were obtained for 18 patients with UC and 21 patients with CD. There was no relationship between disease activity and the number of α2-M-bearing cells. Patients with UC and CD had a greater proportion of immunoglobulin-bearing cells compared with controls but there was no correlation with the α2-M-bearing cells.

These data are in contrast to chronic lymphatic leukaemia where a low serum level of α2-M is associated with an increased proportion of α2-M-bearing cells (James, Tunstall, Parker & McCormick, 1975, Clinical and Experimental Immunology, 19, 237–249).