LETTERS TO THE EDITOR

Phospholipase A_2 in inflammatory bowel disease

EDITOR,—Increased release of pro-inflammatory eicosanoids such as prostaglandin E_2 and thromboxane B_2 from mononuclear cells occurs during relapse in patients with inflammatory bowel disease (IBD).[1] The key enzyme in eicosanoid synthesis is phospholipase A_2 (PLA_2). Raised serum concentrations of the PLA_2 group II isoenzyme can be detected by immunoassay during the acute stages of IBD.[2] We read with interest the recent article by Peterson *et al* about the role of a phospholipase A_2 activating protein, PLAP (*Gut* 1996; **39:** 698–704). The authors showed clearly that PLAP can be detected in monocytes and granulocytes originating from intestinal mucosa of patients with Crohn's disease and ulcerative colitis. In addition to this finding, extracellular deposits of PLAP antigen were associated with blood vessels and oedematous fluid from the inflamed tissue. Peterson *et al* postulated that PLAP may be involved in increasing PLA_2 activity with consecutive eicosanoid generation in IBD. We propose a further possible mechanism of PLA_2 activation during acute IBD in which the pro-inflammatory cytokine interleukin-6 (IL-6) is a key mediator. Peripheral blood concentrations of this cytokine are raised during acute IBD.[3] We showed recently that recombinant human IL-6 alone can increase serum concentrations of PLA_2 group II isoenzyme in humans.[4] Therefore, we suggest that increased IL-6 concentrations during relapse of IBD are also able to induce PLA_2 by a different mechanism from PLA_2 activation via PLAP. The important role of cytokines in the induction of PLA_2 was confirmed by Crowl *et al*,[5] who showed that IL-6 could induce PLA_2 in vitro.

The molecular mechanism of this induction was further elucidated by detection of an IL-6 response element in the promoter region of the PLA_2 gene.[5] In conclusion, activation of PLA_2 by PLAP could be a possible mechanism for increased eicosanoid synthesis in IBD but direct induction of PLA_2 gene transcription by pro-inflammatory cytokines should be taken into account. Therefore, we suggest a study with parallel measurements of IL-6 and PLA_2 serum concentrations during acute relapse of IBD to correlate these parameters and to determine the profiles of occurrence of these inflammation markers. We have developed a radiometric assay which may be useful as a sensitive and reliable method for absolute measurements of the true PLA_2 group II enzyme activity in serum.[6] Parallel measurements using a PLA_2 group II immunoassay may also indicate whether activation or inhibitory factors of PLA_2 are also present in peripheral blood.

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Reply

EDITOR,—The role of cytokines in the formation of lipid mediators involved in cell signalling was recently reviewed, and the interplay among these important substances forms the basis for future development of novel therapeutic approaches for several inflammatory diseases.[1] The proposed mechanism involving the role of IL-6 in elevating group II secretory PLA_2 ($sPLA_2$) in the acute stages of IBD would be consistent with the reported stimulatory effects of pro-inflammatory cytokines (for example, IL-6, IL-1, tumour necrosis factor α (TNF-α)) on eicosanoid generation in cells from various tissues.[1] In murine bone marrow mast cells, IL-10 and IL-1β have been reported to increase expression of type II $sPLA_2$, but not cytosolic PLA_2 ($cPLA_2$).[2] $cPLA_2$ and $sPLA_2$ are two isoforms of the enzyme that have been implicated in inflammation.[3] Arachidonic acid released from membrane phospholipids by the action of PLA_2 becomes the substrate for the cyclooxygenase and lipooxygenase enzymes, which synthesise prostaglandins and leukotrienes, respectively. In human pulmonary epithelial cells, IL-1β, TNF-α, and interferon-γ (IFNγ) cause coordinate induction of both $cPLA_2$ and cyclooxygenase-2 (COX-2) mRNA, resulting in increased prostaglandia E_2 (PGE_2) release.[3] In the human rheumatoid synovial fibroblast, PGE_2 accumulation in response to IL-1β has been shown to be a direct result of coordinated upregulation of the 85 kDa $cPLA_2$ and COX-2.[4 5] TNF-α treatment of human bronchial epithelial cells results in upregulation of $cPLA_2$ gene expression without an effect on $sPLA_2$ gene expression.[6] In normal tissues, arachidonic acid metabolism is regulated by the limited availability of the arachidonic acid substrate, but recently, IL-4 was shown to downregulate levels of $cPLA_2$ mRNA and COX-2 mRNA in mouse parietal bone cultures.[7 8] Further, transforming growth factor (TGF) beta 2 was shown to reduce $sPLA_2$ mRNA levels in rat mesangial cells treated with cytokines and forskolin.[9] The complexity of the roles of cytokines and arachidonic acid metabolites in regulating inflammation is further highlighted by the findings that PGE_2 can (1) upregulate IL-6 mRNA production, and (2) downregulate TNF-α RNA and protein production in different in vitro and in vivo models.[10–12] As discussed in our recent report, PLAP may participate in the intricate control mechanisms that evoke and modulate the actions of cytokines and arachidonic acid metabolites in IBD and other inflammatory diseases. PLAP has been shown to induce IL-2 synthesis in a murine T helper cell line (EL-4)[13] and IL-1 and TNF-α production in human monocytes.[14] The precise role of PLAP in PLA_2 type specificity and enzymatic activity, as well as in the molecular mechanism leading to IBD, remains to be elucidated.

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Effect of L-arginine on intestinal water and sodium absorption

EDITOR,—Wapnir *et al* (*Gut* 1997;**40**:602–7) reported interesting observations on the effect of L-arginine in low concentrations on intestinal water and sodium absorption from rat jejunum, in experiments which they carried out to determine the possible proabsorptive effect of this amino acid if included in oral rehydration solutions. Their results, showing that perfusion of very low concentrations of arginine stimulated sodium and water absorption, but higher concentrations had the reverse effect, recalled to mind observations we made many years ago in the course of a systematic study of the effect of amino acids on sodium and water absorption in human jejunum.[1]

In double lumen intestinal perfusion studies we found that, in contrast with the neutral amino acids glycine and alanine, perfusion solutions containing arginine did not stimulate sodium and water absorption, and at higher concentrations were associated with fluid secretion. We have vivid personal recollection of the choleraic diarrhoea that could be the result. In contrast to the findings in the rat jejunum reported by Wapnir *et al*, no stimulation of fluid absorption occurred in human jejunum at concentrations of arginine as low as 10 mM and 20 mM. The anomalous effect of arginine on sodium and water absorption puzzled us at the time, and it is interesting to speculate that it may be due to nitric oxide induced vasodilatation.

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1 Holdsworth CD, Thirumalai C, Hellier MD. The effect of amino acids and dipeptides on sodium and water absorption in man. *Gut* 1973;**14**:41–5.

Reply

EDITOR,—Hellier and Holdsworth pertinently refer to their pioneering 1973 paper[1] on the effects of certain amino acids and dipeptides on intestinal absorption in humans. L-arginine was studied as a paradigm of a basic amino acid. The secretory response it elicited stood in sharp contrast to the proabsorptive action of glycine, L-alanine and two dipeptides. Furthermore, at 20 mM it produced frank diarrhoeic effects and discomfort. When 10 mM L-arginine was added to isotonic saline, both sodium and water transport were essentially in equilibrium (fig 3 in reference 1). In our experiments with rats, at that concentration, L-arginine had no stimulatory effect, and was indistinguishable from a baseline with no L-arginine. However, a significant difference in the design of the experiments was the presence of a relatively high concentration of glucose (111 mM) in the oral rehydration solutions (ORS) we tested. Other investigators have shown that in the absence of glucose, 20 mM L-arginine abolished net water and sodium absorption.[2] In separate experiments 10 mM glucose neutralised the secretory effect of 40 mM L-arginine.[3] Sodium–glucose co-transport is a key factor that will produce a notable shift in the response of the small intestine to secretory agents, as clearly shown in animal and human studies.[2 3] Hence, the studies cannot be compared directly. Whether the stimulatory effects obtained in rats with low concentrations of L-arginine (1–2 mM) added to ORS can also be observed in humans has yet to be determined.

L-arginine is not the only amino acid known to have a negative effect on fluid and electrolyte absorption. L-tryptophan also has a secretory action[4] and there is evidence that activation of the serotonin pathway is involved.[5] The apparent concentration dependent vasodilator and vasoconstrictor properties of nitric oxide (NO), presumably generated by induction of NO synthase from L-arginine in the small intestinal mucosa, deserve further examination.

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1 Hellier MD, Thirumalai C, Holdsworth CD. The effect of amino acids and dipeptides on sodium and water absorption in man. *Gut* 1973;**14**:41–5.
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BOOK REVIEWS

Cholelithiasis: causes and treatment. Nakayama F. (Pp 298; illustrated; $69.00.) Tokyo: Igaku-Shoin, 1997. ISBN 4-260-14334-4.

Now and again a doctor-scientist becomes so infatuated by gallstones that he gives his or her life to them (a recent example of this rare breed is a Romanian lady). The only cure is to write a monograph. Why do people get this illness? There are many reasons, but money is not one of them. Gallstones make surgeons rich, not scientists. The trouble is gallstones don't kill people, except the occasional academic whose grant application has been turned down for the fifth time. If they did kill people—or if they disabled people or disfigured them—there would be Chairs of Cholelithology and a *Journal of Cholelithology*.

The disease is certainly common enough. In some places it afflicts up to 70% of women if they live long enough. But, despite this, gallstones are a fringe discipline attracting only those of a scholarly bent and with a sense of history. Gallstones have a history all right. Being durable things, they have been found in Egyptian mummies. And they have plagued historical figures in all times. Walter Scott, the novelist, was so racked by pain from his gall bladder he turned his face to the wall and begged to die. In the middle of our own century, four American presidents suffered the same torture and begged to be cut open (Hoover, Truman, Eisenhower, Johnson). You won't learn these facts from this book. It is a book with a laboratory flavour and a distinctly oriental one. For example, it contains all you could ever want to know about hepatolithiasis (ever seen a case?).

In the days when people put up with pain and laughed at stinging nettles, gallstones presented in dramatic ways. Like fistulating right through the abdominal wall. A 19th century GP recalled a breathless child arriving at his door saying "Doctor, come quickly! Grandma's gallstones are rolling down the stairs". In my own professional lifetime patients sometimes failed to trouble the doctor until a large stone had filled the gall bladder with pus, then eroded through its wall and the wall of the adjacent duodenum and then wafted down to the terminal ileum where, finally, it impacted with a sickening jolt—a life-threatening situation ineptly termed gallstone ileus. Again, you won't find this in Nakayama's book—it is not a book for the clinician. It is true there is a chapter on treatment, but it is largely about minority sports like lithotripsy and bile acid therapy.

Part of the trouble is bile. To understand gallstones you have to understand bile, and bile is fiendishly complicated. Bile is like liquorice; you either love it or you hate it, and most people hate it. But some, like Nakayama, are fascinated to distraction by its kaleidoscopic contents and their subtle interactions. Once we all thought gallstones could be explained by plotting of three of bile's constituents on a triangle and seeing where the value lay—above or below a magic line which represented the cholesterol-holding capacity of bile. Now we know there is a host of factors determining whether bile flows serenely on its way or whether it starts insidiously dropping crystals of various shapes. We know too that lots of factors determine whether the gall bladder manages to flush out these crystals or is left with irritating, gritty lumps lying in wait till the evil day when they impact in the neck of the gall bladder or the common bile duct—and cause mayhem. If this is the sort of thing you want to know about, then this book is for you. It is very strong on the biochemistry behind gallstones, quite strong on the biophysics and the physiology. It also parades many facts on the epidemiology of gallstones (but, curiously, ignores the best British work). All in all, it is a great repository of arcane knowledge as it was in 1993/94, when the references stop.

Nakayama earns 9 out of 10 for scholarship but, I fear, barely 1 out of 10 for presentation. In this age of marketing one wonders about the input of his publishers. To attract new converts bile and gallstones need the tricks of the salesman. No way does this book provide them. Rather, it bludgeons the brain. Dense blocks of text up to two pages long cry out for paragraphs, subheadings, pithy summaries and illustrations. And look elsewhere for wit and humour.

So who is this book for? Not for beginners, unless they have the stamina of a marathon-runner. Nor for researchers wanting the latest advances and a glimpse into the future. Only I suspect for scholars wanting comprehensive coverage and a massive bibliography. They, however, will be in clover.

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Clinical Pathology of Pancreatic Disorders. Edited by J A Lott. (Pp 218; $99.50.) Totowa, New Jersey: The Humana Press, 1997. ISBN 0-896-03475-5.

Pathologists think themselves very good at classifying things, but they're not even good at classifying themselves. In the United Kingdom, "pathologist" sometimes means histopathologists only, and sometimes bacteriologists, chemical pathologists and haematologists, too. As a histopathologist, I think that what I do is very clinical, but in many parts of the world, I'd be labelled an "anatomic pathologist", a "morbid anatomist", or even both, to distinguish me from "clinical" pathologists. I rather like to label the latter "fluid" pathologists, if only because my discipline becomes, by way of contrast, "solid" pathology. The United Kingdom and continental Europe have contrasting practices, and both differ from North America. The American publishers of this book expect its readers to include "laboratory medicinists"—and I've never even heard of them!

You can see, therefore, that I didn't know what to expect from a book on "clinical pathology", and my first task was to determine what disciplines it covered. There's a little immunology, with insights into pancreatic transplantation and the aetiology and pathogenesis of diabetes mellitus. Histopathology is largely ignored, even in the chapter on pancreatic neoplasms, and there is very little discussion of the bacteriological complications of acute pancreatitis or the putative viral triggers of type I diabetes mellitus. However, there is a great wealth of detail on the role of clinical biochemistry in the diagnosis of pancreatic diseases, both exocrine and endocrine, and their complications, together with a more patchy coverage of the biochemical pathogenesis of these conditions. The former component is excellent, the latter focally disappointing: I think—for example, that a book that discusses assays of pancreatitis associated protein in the diagnosis of acute pancreatitis might also clarify recent developments in the role of the closely related lithostathine/stone protein in the pathogenesis of chronic pancreatitis.

This book reads like five long review papers, rather than a single integrated text. This is not a problem if you want to bring yourself up to date on some broad field or other, but it is disconcerting if you simply want to look up a single topic, especially with the brief and unhelpful index. There is no cross-indexing so that, for instance, you'll only find "alpha-fetoprotein" and "carcinoembryonic antigen" if you look up "tumour markers", and some of the references to elastase are under "E", while the remainder reside under "P" (for "pancreatic enzyme").

So what does this book have to offer the gastroentrologist? It'll provide a significant amount of irritation and tedium if, like me, you try to read it from cover to cover. It won't help a lot if you're hoping for help with the day-to-day investigation of pancreatic disease. It will enable you to seem relatively well-informed if you hope to enter dialogue about future strategies in test selection with your local chemical pathologists (and I think it appropriate and important that you do). While you're there, ask them to classify themselves.

EMYR W BENBOW

NOTES

International Workshop on Variceal Haemorrhage

The International Workshop on Variceal Haemorrhage will be held in Hong Kong on 1–2 December 1997. Further information from: Professor Joseph Sung, Endoscopy Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong. Tel: +852 2632 2233; Fax: +852 2635 0075.

12th International Workshop on Therapeutic Endoscopy

The 12th International Workshop on Therapeutic Endoscopy will be held in Hong Kong, from 2 to 4 December 1997. Further information from: Professor Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong. Tel: +852 2632 2233; Fax: +852 2635 0075.

Second International Conference on Therapies for Viral Hepatitis

The Second International Conference on Therapies for Viral Hepatitis will be held in Kona, Big Island, Hawaii, from 15 to 19 December 1997. Further information from: Dora Moya, International Medical Press, 3112 E. Shadowlawn Ave., Atlanta, GA 30305, USA. Tel: 800 868 2022 or 404 233 0261; Fax: 404 233 2827; Web site: www.intmedpress.com/hawaii/.

Course in Postgraduate Gastroenterology

A Course in Postgraduate Gastroenterology will be held in Oxford, UK, on 4–7 January 1998. This course has been designed for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include:

- Liver disease
- Colonic neoplasia
- Acute pancreatitis
- Osteoporosis, arthritis and GI disease
- Food allergy and intolerance.

Course fee £200 ($330). Board and accommodation are available at Wadham College at extra cost. Six bursaries will be available for applicants training in gastroenterology or in research posts at British hospitals. Further information from: Dr DP Jewell, Gastroenterology Unit, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.

Colorectal Disease in 1998

The 9th Annual Colorectal Disease in 1998: An International Exchange of Medical and Surgical Concepts will be held at Marriott's Harbor Beach Resort, Fort Lauderdale, Florida, USA, from 19 to 21 February 1998. Further information from: Cleveland Clinic Florida, Department of Education, 2950 West Cypress Creek Road, Fort Lauderdale, FL 33309-1743, USA. Fax: 954 978 5539; Other: 800 359 5101, ext 5056; Local/international: 954 978 5056: email: jagels@cesmtp.ccf.org.

6th Southeast European Congress of Paediatric Surgery: Short Bowel Syndrome

The 6th Southeast European Congress of Paediatric Surgery: Short Bowel Syndrome will be held in Graz, Austria, on 22–23 May 1998. Further information from: Dr Günther Schimpl, Department of Paediatric Surgery, Auenbruggerplatz 34, A-8036 LKH-Graz, Austria. Tel: +43 316 385 3762; Fax: +43 316 385 3775.

9th British Association of Day Surgery Annual Scientific Meeting

The 9th British Association of Day Surgery Annual Scientific Meeting and Exhibition will be held at the Harrogate International Centre, Harrogate, UK, on 4–6 June 1998. Further information from: Kite Communications, The Silk Mill House, 196 Huddersfield Road, Meltham, West yorkshire HD7 3AP, UK. Tel: 01484 854575; Fax: 01484 854 576; email: info@kitecomms.co.uk.

9th International Symposium on Cells of the Hepatic Sinusoid

The 9th International Symposium on Cells of the Hepatic Sinusoid will be held in Christchurch, New Zealand, from 27 September to 1 October 1998. Further information from: Professor Robin Fraser, I.S.C.H.S., Christchurch School of Medicine, PO Box 4345, Christchurch 8001, New Zealand. Tel: +64 3 3640 587; Fax: +64 3 3640 593; email: grogers@chmeds.ac.nz.

Growth Factors and Nutrients in Intestinal Health and Disease

An International Symposium on Growth Factors and Nutrients in Intestinal Health and Disease will be held at the Rihga Royal Hotel, Osaka, Japan, from 31 October to 3 November 1998. Further information from: Kinya Sando, MD, Department of Pediatric Surgery, Osaka University Medical School, 2-2 Yamadoaka, Suita, Osaka 565, Japan. Tel: +81 6 879 3753; Fax: +81 6 879 3759; email: gut@pedsurg.med.osaka-u.ac.jp.

Advanced Course in Gastroenterology

An Advanced Course in Gastroenterology will be held at the Royal College of Physicians of Edinburgh, UK, from 3 to 7 November 1998. Further information from: Miss Lee Ross, Symposium Assistant, Education, Audit and Research Department, Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 1JQ, UK. Tel: +44 131 225 7324; Fax: +44 131 220 4393.