Correspondence

Portal and mesenteric thrombosis revealing constitutional protein C deficiency

SIR,—We read with interest the article of Valla and colleagues in the June issue (*Gut* 1988; **29:** 856–9). We had to deal with a similar case when in May 1984, a 49 year old woman was admitted to our hospital for a small bowel obstruction. At the subsequent laparotomy, 1 m ileum was found necrotic and the histological examination of the resected bowel showed an ileomesenteric infarction. Peroperative liver biopsy showed no abnormality. The presence of splenic, mesenteric and portal veins thrombosis was assessed by means of ultrasonographies, CT scan and coelio-mesenteric arteriography. Three small oesophageal varices were noticed at endoscopy. An extensive bilateral phlebitis of the legs occurred in the postoperative period and was treated by heparin, and a Greenfield caval filter device was implanted. Haemostasis and coagulation investigations, including antithrombin III, were found normal, but measurement of protein C was not carried out. In April 1985, the patient was readmitted after three episodes of gastrointestinal bleeding. Varices were large. Liver function tests, platelet count, prothrombin and cofactors, antithrombin III and protein S antigen were all found in the normal range. Myelogram showed well balanced myeloid populations. Protein C antigen (immunoenzymatic) was found decreased at 39% (n=70–120). To prevent recurrence of variceal haemorrhage, a trans-section of the oesophagus was done, followed by a new phlebitis of the left leg, treated with heparin and then calciparin. In December 1985, a recurrence of variceal bleeding as a result of a rupture of residual varices of the lower oesophagus required treatment by sclerotherapy for six months. Follow up was satisfactory and the patient has not suffered from phlebitis or gastrointestinal bleeding since. The patient never received antivitamin K (AVK). Protein C, controlled in October 1987, was still very low in activity at 40% and slightly lowered in antigen at 59%. An inquiry in 1987 in the patient's family with measurements of protein C antigen showed that, among the four children and the three brothers and sisters of the proband tested, only one son had a slightly decreased protein C antigen rate (63%), while his protein C activity was normal. None of the proband's relatives had a clinical history of thrombosis.

Constitutional protein C deficiency is still generally considered to be responsible for venous thrombosis of the lower limbs, pulmonary embolism, and sometimes thrombosis of the mesenteric vein. Yet, in the recent series of Green *et al*,[1] two cases of splanchnic venous thrombosis with protein C deficiency were probably constitutional deficiencies. Valla and colleagues' case report and our own case confirm that constitutional protein C deficiency is probably not exceptionally engaged in the pathogenesis of chronic portal thrombosis. Other works by Valla *et al*,[2] however, suggest that proteins C and S deficiencies should not explain the majority of 'idiopathic' portal thrombosis. Nevertheless, we agree with the authors that measurements of proteins C and S, now easily feasible in most centres,[3] should be carried out in patients with portal thrombosis when no overt cause is present. An interesting point is the prevention of recurrent variceal haemorrhage in those patients. The authors suggest the use of β-blockers against portal hypertension, arguing with relevance that it is compatible with AVK. Our patient has been doing well for three years after sclerotherapy but she did not receive AVK because she was protected against pulmonary embolism by her Greenfield filter. The problem seems to put in the balance the risk of bleeding from postsclerotherapy ulcers if the patient is treated with AVK and a therapy, propranolol, whose efficiency might not be as satisfactory as sclerotherapy.

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Nicotine and ulcerative colitis

SIR,—Cigarette abstinence is sometimes a feature of ulcerative colitis, and perhaps of some cases of Crohn's disease. Behavioural regulation of physiological homeostasis is well known, and influences many needs such as alleviation of hunger and thirst. A proposal that cigarette smoking is symptomatic of one or more physiological deficiencies in bio-

genic monoamine neurotransmitter endocrinology that nicotine tends to alleviate has been widely ignored, overlooked, and subjectively rejected. Could adrenalin deficiency, for example, contribute to the risk of ulcerative colitis? Because epidemiological (statistical) correlation is incapable of distinguishing cause from symptom, as inference of causality from correlation, though popular, is an example of statistical malpractice, and as personal opinion or ideology cannot be equated with fact, it is urged that the hypothesis that smoking is symptomatic of a physiological deficiency that nicotine tends to alleviate be evaluated objectively, fairly, and without puritanical or other bias.

In an extensively documented discussion of ulcerative colitis (UC) and Crohn's disease (CD), Tysk *et al*[1] considered the relationships of tobacco smoking to these afflictions. They noted reports that non-smoking was a characteristic of UC and possibly of CD. Biochemical and endocrinological questions pertaining to nicotine were not examined.

It should be noted that Bowers *et al*,[2] in examining the question of whether cigarette smoking may be an example of behavioural regulation of physiological homeostasis, cited a number of reports on non-smoking as a feature of UC that were not cited by Tysk *et al*.[1] Among these reports are those of Jick and Walker,[3,4] Roberts and Diggle,[5] Harries *et al*,[6] de Castilla,[7] Bures *et al*,[8] Gyde and Allan,[9] Bailar,[10] and Bowers *et al*.[11]

Based on observed evidence, UC may well be a 'nicotine-deficiency' affliction which, for some, is alleviated by nicotine.[2] Richter[12] cautioned that the effort to maintain a constant internal environment or homeostasis 'constitutes one of the most universal and powerful of all behavioral urges or drives.'

The relationship of nicotine to endocrinology, involving hormones such as adrenalin and noradrenalin, was noted.[2] A concept of treatment of certain genetically-based hormonal deficiencies with nicotine was proposed.[13] Objections were expressed by Wilke[14] and Slade.[15] As was noted,[16] however, subjective disapproval cannot reject an hypothesis scientifically. Causality or benefit must be based on scientific evidence, not on authority, opinion, ideology, nor on misuses of statistics.[16]

It is noteworthy that recent reports on the use of nicotine containing chewing gum as a means of minimising or stopping smoking[17–19] ignored the concept or hypothesis that use of nicotine, or smoking, is a behavioural regulatory means of normalising physiological homeostasis.[2,13,16] Part of the problem arises from abuses and misuses of statistics and of science.[20,21]

As was pointed out,[2] the concept that smoking is symptomatic of a physiological need that nicotine tends to alleviate is generally ignored. The concept should be evaluated without bias, without imposition of personal opinion, without selective reporting, without misused statistics, without influences of politics and ideology, and without the equating of personal opinion with fact.

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Pancreatitis from intestinal reflux – Again?

SIR,—Twenty years after the publication in *Gut* of McCutcheon's 'fresh approach' to the pathogenesis of acute pancreatitis,[1] we now have Keynes' 'heretical thoughts' (*Gut*, 1988; **29:** 1413–23). Both articles are highly polemical essays promoting the intestinal reflux theory, especially for acute pancreatitis from gall stones. Keynes now offers the readership of *Gut* his intestinal bacteria hypothesis,[2] namely that gall stones cause haemorrhagic pancreatitis only when migration of the stone across the ampulla causes Sphincter of Oddi incompetence allowing for duodenopancreatic reflux containing '. . . cytotoxin producing bacteria or toxic bacterial products . . .' which cause acinar cell necrosis and haemorrhage.

Yet clinical experience is at variance with the intestinal reflux theory. First, surgical sphincteroplasty[3] and endoscopic sphincterotomy[4] though further rendering the Oddic sphincter in effect even more incompetent[5] or ablating it altogether improve rather than worsen acute gall stone pancreatitis as would be predicted by the intestinal reflux theory. Moreover, longterm studies of sphincteroplasty for gall stone pancreatitis reveal a low[6] to absent[3] incidence of recurrence, contrary to the expectation of the intestinal reflux theory. In addition, recurrence of pancreatitis after surgical sphincteroplasty for non gall stone pancreatitis is not known to be more severe than that occurring in the absence of surgery,[7] so a critical role for refluxed bacteria as promoters of haemorrhagic pancreatitis seems highly unlikely, although in some cases, there might be a contribution of resident pancreatic flora[8] to pancreatic sepsis occurring in haemorrhagic pancreatitis; an often lethal combination.[9]

Keynes correctly argues that lethal haemorrhagic pancreatitis does not occur simply from ductal obstruction which only causes reversible oedema, fibrosis and acinar atrophy in experimental settings,[10] as well as in man.[11] This, however, does not exclude obstruction as the beginning of the progression to haemorrhagic pancreatitis, only that it is exceptional, occurring in no more than 15% of patients, even of those who die of acute obstructive (gall stone) pancreatitis,[12] and not at all in aminals with experimental ductal obstruction.[10]

A factor likely to be important in the progression to haemorrhagic pancreatitis although not considered by Keynes, is the vascular response to obstruction.[13] In animals with an intact pancreatic vasculature, when interstitial ('oedematous pancreatitis') is experimentally produced, there is an associated increased perfusion.[14,15] When the vasculature is experimentally impaired in the presence of ductal obstruction and oedema, however, haemorrhagic pancreatitis occurs.[16] Decreased perfusion is also observed in conjunction with oedema and vascular injury, potentially serving to further promote haemorrhagic pancreatitis.[15] In the absence of vascular impairment, haemorrhagic pancreatitis does not occur with ductal obstruction presumably because of adequate perfusion.

The variable pancreatic injury found at surgery and autopsy in acute gall stone pancreatitis is explicable in terms of the vascular response to obstruction and the duration of the obstruction, with haemorrhagic pancreatitis being exceptional, occurring only when pancreatic perfusion is inadequate to maintain oxygenation and nutritive support of acinar cells in the face of oedema.

Fortunately, in gall stone pancreatitis the transient nature of obstruction[17] typically occurring from very small calculi[18] coupled with an adequate vascular response may allow for what is usually a selflimited episode.[17] More prolonged obstruction, however, particularly in elderly patients who are at greatest risk for an inadequate vascular response may be a predisposing factor for an adverse outcome,[19] but one which can be reversed with timely intervention to relieve the obstruction.[20]

Obstruction, therefore, which in exceptional circumstances leads to ischaemic necrosis, rather than reflux of cytotoxin producing bacteria, is a more likely mechanism for the widespread acinar cell necrosis recognised at autopsy in haemorrhagic pancreatitis. It is tempting to speculate that if the ischaemic necrosis were massive enough, trypsinogen might be present in necrotic acinar lobules in excess of inhibitors, at a pH and calcium concentration favouring autoactivation.[21] Alternatively, in the presence of the severe acute inflammatory response which occurs with parenncymal necrosis,[22] trypsin activation could occur from leucocyte derived cathepsin.[23] Either mechanism may further serve to activate elastase,[24] phospholipase A,[25] and the bradykinin system,[26] further serving to impair pancreatic perfusion and cause additional parenchymal necrosis as well as to promote the systemic absorption of activated enzymes which both in animal models,[27] and man[28] is associated with the multisystem failure[29] seen before death from haemorrhagic pancreatitis.

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