one reported in this issue of Gut, may yield the most fruitful information.11 15

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Pepsinogen genetics and duodenal ulcer disease

SIR.—We were pleased to read that our work on the genetics of serum pepsinogen and duodenal ulcer (DU) disease has been essentially confirmed in an Indian population by Habibullah and colleagues (Gut 1984; 25: 1380–3). While Habibullah et al used a proteolytic assay to determine total serum pepsinogen, and we used a radioimmunoassay for the separate determination of serum pepsinogens I and II, both studies found that healthy first degree relatives of hyperpepsinogaenic DU patients have serum pepsinogen values intermediate between the patients and controls, and that the segregation of hyperpepsinogaenia is consistent with autosomal dominant inheritance in many families.1–3

We take issue, however, with the assertion of Habibullah and colleagues that total serum pepsinogen is a better marker of DU than serum pepsinogen I. There is no published evidence to support this proposal. The testing of this hypothesis would require the determination of serum pepsinogen by both proteolytic assay and radioimmunoassay in the same population. Further, our data do not support the proposal by Habibullah et al that DU disease can be divided simply into a genetic hyperpepsinogenic form and a non-genetic normo-pepsinogenic form. In European and North American populations, we have found aggregation of DU and an increased frequency of DU among the relatives of families identified through index cases of DU with normal serum pepsinogen I levels.2 3 We have also found that several pathophysiologic abnormalities characteristic of DU aggregate in some families with DU and normal concentrations of serum pepsinogen I.

Our studies, as well as those of Lam and coworkers, have shown that the genetic heterogeneity of DU disease extends beyond that which can be defined by normal and raised concentrations of serum pepsinogen I.4–7 Our earlier studies have shown that antral G-cell hyperplasia,8 9 characterised by DU, hypergastrinaemia and hyperchlorhydria, has a familial basis.10 11 We have found that rapid gastric emptying may be another inherited physiologic defect in DU associated with normal concentrations of serum pepsinogen I.12 There is also evidence that in some DU families, gastroduodenal inflammation is a concomitant, and even possibly a precursor of ulcer disease. This can be assessed non-invasively by the pepsinogen I/II ratio. Familial aggregation of low PG I/PG II ratios, a highly sensitive marker of gastritis,13 14 has been observed in some DU and gastric ulcer families.4

It is likely that both hyperpepsinogaenic I and normopepsinogaenic I DU disease have multiple underlying causes. Some of these are genetically determined, whether autosomal dominant, autosomal recessive, or polygenic, and some may be primarily environmental. Habibullah and colleagues propose that the normopepsinogaenic form of DU has only a non-genetic aetiology. This may be valid for the Indian population; however, it was not
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clear from their data that a genetic interpretation of normoepisynogenaemic DU could be rejected in other populations. In other populations we have developed considerable evidence that normoepisynogenaemic I DU may be composed of both genetic and non-genetic forms.

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References


Reply

SIR.—Our studies in an Indian population using a proteolytic assay to determine total serum pepsinogen revealed that healthy first degree relatives of hyperpepsinogaenemic duodenal ulcer (DU) patients have serum values intermediate between the patients and controls. It was also concluded that the segregation of hyperpepsinogenaemia is consistent with an autosomal dominant mode of inheritance in the families of these patients.

From the results obtained by us we concluded that total serum pepsinogen may be a better serum marker of duodenal ulcer. In order to support this speculation in our publication we cited the reference of Mirsky who observed a tendency for higher values of total serum pepsinogen among patients with active lesions using the same proteolytic assay used by us in our study. In fact we are planning to take further studies to test our hypothesis by determining serum pepsinogen by both proteolytic assay as well as radioimmunoassay in the same population. So far as the division of DU cases into a genetic hyperpepsinogenenaic form and a non-genetic normoepisynogenaemic form is concerned, it was based on two observations. Firstly, we found no familial aggregation of DU disease in our cases with normoepisynogenaemia. The second observation that lead us to this conclusion was a high frequency (54-2%) of ‘O’ blood group among DU patients with hyperpepsinogenaemia compared with a relatively very low frequency (23.52%) of this blood group in normoepisynogenaemic patients. Further, a careful perusal of our paper reveals that our conclusion with regards to a non-genetic basis for DU disease with normoepisynogenaemia was tentative as we admitted that the number of such cases (DU cases with normoepisynogenaemia) was limited (refer page 1383, second paragraph). We hope this clarifies the issue raised.

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