Pepsinogen

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Introduction

In 1951 life for the student of pepsinogen was quite simple. We believed we had learned most of what we needed to know in the 115 years since the first discovery and naming of pepsin by Schwann in 1836*. In 1880 Heidenhain reported that the gastric mucosa contained specialized cells which, respectively, secreted acid and pepsin; and in 1881-1886, Langley performed and reported his classical experiments describing the cycle of the zymogen cells and their granules. He also defined and crystallized the precursor of pepsin, pepsinogen, which he recognized to be the contents of the granules of the peptic cell.

The first assignment Avery Jones gave me was to study 'uropepsin', first described by Brucke in 1861, and the subject of a recent revival of interest (Mirsky *et al.*, 1948). What made it worth restudy was the availability of a reliable method for measuring proteolytic activity by the timed digestion of acidified haemoglobin (Anson and Mirsky, 1932). This method could be used to measure with relative ease pepsin in urine, blood and gastric juice as well as in other fluids or tissue extracts; the same method is still widely used and is the standard by which the activity of commercially available pepsin(ogen) is measured (Sigma Chemical Co.).

In 1951 we knew that pepsinogen was a protein of molecular weight (mol. wt). 43,000 and that it was activated to pepsin by acidification with the loss of a number of peptides, totalling about 5,000 mol.wt. (Northrop, Kunitz and Herriot, 1948). At that time we knew that pepsinogen occurred in all stomachs, but it was believed to be a molecule of the same weight and structure in all species. The histology of the peptic cell in mammals and the combined cell in submammals was known from light microscopy. However, the processes whereby protein was synthesized, transported in the cell and excreted were poorly understood, and the structure and function of DNA and RNA were still unknown. Improved quantitative methods had begun to define the rates of secretion, and we knew only two stimuli: the vagus

via acetylcholine, and histamine. Gastrin was still a theoretical secretagogue, and the Zollinger-Ellison syndrome was yet to be described. We had only one specific antagonist, atropine, though we did know that the recently discovered antihistamines did not antagonize the gastric effects of histamine. Between those who studied man and those who studied cats and dogs, there was much argument as to whether histamine did or did not stimulate pepsin secretion. Both were right, of course. The measurement of uropepsin and the nearly contemporaneous Azure-A tubeless gastric analysis were seen as providing diagnostic shortcuts to objectively diagnose upper gastrointestinal (GI) disease, including gastric cancer and peptic ulcer, and to sort out the ulcer-prone (Mirsky *et al.*, 1948).

Since 1951, the study of pepsinogen has benefited from spectacular advances in molecular biology, cell biology, protein chemistry, knowledge of drugs, hormones, and receptors, in cell separation, immunology and tissue culture.

In these intervening years we have learned that there are many major and minor structural and size variants of pepsinogen; the genes for human, rat and swine pepsinogen have been identified, and the amino acid sequences of many pepsinogens are known. Pepsinogens have been classified by electrophoretic mobility and immunological characteristics; this classification has been further amplified by cellular and anatomic localization, and by distribution in blood, semen and urine. These findings have been related to disease and heredity.

Developments in the field of neurohormonal control of secretion have illustrated the complexity of the integrative physiology of digestion. The workings of protein-secreting cells are better known; receptors have come under intense and systematic study, and new drugs have made such studies easier and more specific. Finally peptic ulcer disease is better understood and better defined.

Studies of pepsin have advanced knowledge on two parallel tracks. On the one hand, we know more about protein synthesis and secretion in general and protein enzymes in particular. On the other hand, the

*For historical references see Hirschowitz (1957).

application to diagnosis and understanding of upper GI disease has progressed, perhaps more slowly, since other technologies in diagnosis and treatment have tended to overshadow pepsinogens.

What follows is a brief presentation of the present status of the chemistry, cell biology, physiology and pathophysiology of pepsinogen.

Chemistry

Pepsinogen, the inactive precursor of pepsin, is secreted from peptic cells. In an acid medium, through a multistage process, pepsinogen is converted to pepsin by a loss of the N terminal sequence consisting of a variable number of amino acids (Kageyama and Takahashi, 1980a, b); further conformational changes occur in the remaining protein to expose two catalytic sites (Tang, 1977). The activation of pepsinogen is slow at pH 6.0, but extremely rapid at pH 2 or less. The activation peptide and analogues of this peptide have some anticatalytic activity, but this is of no practical consequence in the protein digestive function of pepsin in the stomach.

Once activated, pepsin is liable to irreversible denaturation at pH above 7.2, by temperatures above 65°C, and by high concentrations of urea. In contrast, pepsinogen is not denatured by pH as high as 10 or at temperatures up to boiling in salt-free solutions. This difference in alkali denaturation led Langley a century ago to distinguish pepsinogen from pepsin.

Pepsin digests protein with a pH optimum for digestion of haemoglobin or albumin of 1.8 to 2.3, but as has been known for many years, the acid-active gastric proteases have a wide optimal pH range. The other most clearly identified acid protease with a pH optimum of about 2–3.5 was called cathepsin; and yet another protease, gastricsin, exhibits a pH optimum of 3.2. However, the pH optimum of pepsin for different substrates may vary, thus milk clotting, another action of this enzyme, occurs at pH 5.5. The chemistry of protein hydrolysis has been extensively reviewed (Tang, 1977).

Pepsinogen can be electrophoretically separated into multiple bands representing decreasing electronegativity or anodal mobility (Richmond *et al.*, 1958; Seijffers, Segal and Miller, 1963; Kushner, Rapp and Burtin, 1964; Samloff, 1969). There appear to be about seven pepsinogens (Pg 1–7) that conform to the operational definition of inactive precursors resistant to alkaline pH, but which, upon acidification, convert to acid active proteases with pH optima near 2.0 and susceptibility to inactivation above pH 7.2. Each of the seven (or more) pepsinogens apparently give rise to a unique and equivalent pepsin. These seven pepsinogens may be grouped immunologically into

two groups, pepsinogen I and II (PGI and PGII) against which specific and non-crossing antibodies can be developed. PGI comprises Pg 1–5 and PGII, Pgs 6 and 7.

Such a classification appears to be further validated by the anatomic distribution in the stomach, antral and duodenal mucosa and the 2–3 cm of cardiac glands surrounding the oesophagogastric junction contain only PGII, while the main body of the stomach contains both PGI and II with PGI predominating. Furthermore, while serum contains both PGI and PGII, urine contains only PGI (uropepsin) and semen only PGII, originating in the prostate. Before 32 weeks gestation, human amniotic fluid contains PGI, and from 32–40 weeks, both PGI and II. Moreover, PGI and II have different peptide bond specificities with artificial dipeptide substrates (Samloff, 1983), e.g. I > II for tyrosyl-phenylalanine, but II > I for tyrosyl-alanine, -threonine, -leucine, and -serine. The catalytic rate ratio of PGI and PGII for bovine haemoglobin is 3:4, while egg albumin is digested by both at a much lower rate in the ratio of 0.25:0.1. The pH optima for PGI range from 1.5 to 2.0, and for PGII (gastricsin), the pH optimum is 3.2. PGI is more sensitive to denaturation by alkali (pH 7.2 vs pH 8.0 for PGII) and less so to heat (PGI 16% vs PGII 80% at 62°C after 15 min at pH 2.4) (Samloff, 1983).

Thus, there is much diversity in proteolysis depending on substrate, pH, temperature, solute and substrate concentration. Some methods for quantitation of pepsinogen are insensitive and probably provide quite inadequate data, e.g. radial diffusion (see Ishague and Bardhan, 1978) and studies that use egg albumin or casein substrate or those that depend upon milk-clotting. The use of haemoglobin substrate at pH 2.0 is still recommended as an inexpensive assay with a long and reliable history (Anson and Mirsky, 1932).

Heterogeneity of pepsinogens is apparently due to substitutions at the N-terminal end (Kageyama and Takahashi, 1980a, b, c). However, immunological grouping of PGI and PGII remains valid across species with differing N-terminal sequences or even with pepsinogen of different sizes; thus the unusually low molecular weight frog pepsinogen reacts with human PGI antiserum (Shugerman *et al.*, 1982).

The original belief that all pepsinogens and pepsins were nearly the same size was disproved by the finding from my laboratory of a pepsinogen of mol. wt. 29,000 daltons (Shugerman *et al.*, 1982). We also found that pepsinogens from several species, including crustaceans, amphibians, fish and mammals varied from 29,000 to 65,000, unpublished values which are outside the general range of 35,000 to 48,000 daltons described for mammals and birds (Yasugi and Mizuno, 1981). As well, Yasugi

and Mizumo described a chicken-embryo specific-pepsinogen of mol. wt 56,000 and corresponding pepsin of 53,000, which resemble adult pepsinogen in its alkali stability and optimal pH, but differed in sensitivity to inhibition by pepstatin and its antigenicity. Human fetal pepsinogen is also different from that in the adult. It is of some interest that a fetal type pepsinogen has been isolated from a gastric cancer (Hirsch-Marie *et al.*, 1976).

Pepsinogens from various species have been sequenced (Kageyama and Takahashi 1980a, b, c; Muto *et al.*, 1980). Even more importantly, the gene for human pepsinogen has been identified (Sogawa *et al.*, 1983) from a recombinant clone using swine pepsinogen cDNA as a probe. It occupies 9.4 kilobases of DNA and comprises 9 exons and 8 introns of various lengths, and produces a 373 amino acid protein that is 82% homologous with swine pepsinogen. As a matter of particular interest, there is a 15-amino acid residue at the NH₂ terminus indicating that the pepsin precursor is synthesized, like many other proteins, as a *pre-pepsinogen*. The two homologous sequences, including the two active site aspartyl residues present in different coding segments, suggest that the pepsinogen gene evolved by duplication of a shorter ancestral gene. Ichihara, Sogawa and Takahashi (1982) used rat gastric mucosa RNA to produce rat pre-pepsinogen with a 16 amino acid extension at the NH₂ terminal. They also reported molecular cloning of complementary DNA to swine pepsinogen mRNA (Sogawa *et al.*, 1981). Since the synthesis of protein depends on the production and control of mRNA, the key to further understanding of the action of stimuli of pepsinogen secretion lies in understanding fully how secretion and secretagogues affect the synthesis and turnover of mRNA in the peptic cell.

Biology of the peptic cell

The peptic cell shares with all exocytotic cells most of the processes leading from stimulation to secretion. Thus secretagogues interact with specific receptors to initiate either acute cationic movements or the stimulation of adenylcyclase to produce cAMP. A further series of steps involving calmodulin, protein kinases and the cytoskeleton lead ultimately to the release by exocytosis of products stored in encapsulated packets.

The steps from the activation of second messengers leading to secretion of protein product are at present not clearly understood. There are probably three major events involved: (1) the prompt release of stored cell product; (2) stimulation of new synthesis and sustained secretion of product; and (3) the uptake of amino acids. The first process, which is probably Ca⁺⁺ dependent, must involve conjunction

or fusion of the zymogen granule membrane with the cell membrane, the reduction in surface tension at the site of adherence and the thinning and the ultimate opening of the granule interior to the outside of the cell with discharge of granule contents. Since it is not clear that the granule contents are under pressure, the release of these contents must be an active process, achieved either by the flow of the rest of the granule membrane to the level of the cell membrane (trampoline phenomenon) or an unseen action of contractile elements (slingshot phenomenon). The mechanisms whereby the granule approaches the membrane is unknown; the best bet is again the contractile elements of the cytoskeleton, activated via Ca⁺⁺, calmodulin and protein kinase. I know of no data describing changes in either membrane which precede or which would promote fusion. At any rate, the fusion of the zymogen granule and cell membranes under stimulation (exocytosis) begs the question of which forces, electrostatic or other, normally keep granules from fusing with each other or with the cell membrane and how, for example, atropine would cause the cell to become overstuffed with granules without granule fusion. These granules stay the same size, but increase greatly in number; even so, the granule and cell membranes still remain unfused and secretion is much diminished (Hirschowitz, O'Leary and Marks, 1960). Also unknown is whether, after exocytosis, the fused granule membrane is recycled to new granules or whether all granule membranes are synthesized *de novo*.

The second major effect of stimulation upon the secreting cell is to initiate the process of sustained protein secretion. This step is probably more dependent upon cAMP. This sequence of events is even less well understood than exocytosis, because we do not know whether the receptors act from the surface or are internalized, whether they act in the cytosol or in the nucleus. We know from general principles that mRNA is produced and that mRNA in turn migrates to the very abundant rough endoplasmic reticulum (RER) where protein, in this case prepepsinogen, is produced and transported by an unknown method to the Golgi apparatus where it is encapsulated (Hirschowitz, 1967a, b). However, during prolonged active stimulation, granules are depleted, suggesting that newly synthesized pepsinogen may be rapidly transported and secreted without passing through the granule or storage stage. The intracellular pathways for such a phenomenon are not well delineated, though most likely the microtubular system of the cell is involved.

The uptake from interstitial fluid or medium of the amino acids used in protein synthesis must also be stimulated. We do not know whether there are specific transport mechanisms or requirements, such as Na⁺, for the uptake of amino acids and how, after

passing the basolateral membrane, these amino acids are directed or transported to the site of protein synthesis.

These questions should be much more readily answerable now that isolated peptic cells can be arranged in single cell thickness sheets on a collagen matrix with tight junctions and vectorially oriented and can be shown to exhibit appropriate resistance and potential difference measurements (Ayalon *et al.*, 1982).

Pepsinogen is secreted by specific gastric mucosal cells in mammals, the chief cells of Heidenhain, whereas in birds, fish, amphibia and reptiles, pepsinogen is synthesized and secreted in the same cells that secrete HCl. One interesting exception is the localization of dedicated peptic cells in densely packed glands in the lower oesophagus of frogs. In the stomach of frogs, however, as in other submammals, pepsinogen is also secreted in the mixed function acid-secreting oxyntic cells. Pepsinogen II is also secreted in much smaller amounts by antral and prostatic cells.

Studies in *in vitro* tissues have begun to identify various stimuli of pepsinogen secretion and to suggest second messenger pathways. In isolated rabbit and guinea-pig glands, cholecystokinin (CCK), but not secretin (Koelz *et al.*, 1982), is a potent stimulus, while caerulein and gastrin G-17 are about 1/10th as potent. However, these peptides are equipotent with CCK as stimuli of acid secretion (Hersey, May and Schuberg, 1983). Cholinergic stimulation is reported for all preparations (Koelz *et al.*, 1982; Hersey *et al.*, 1983; Simpson, Goldenberg and Hirschowitz, 1980) as is isoproterenol (Koelz *et al.*, 1982; Hersey *et al.*, 1983; Shirakawa *et al.*, 1983), a weaker stimulus. Both are blocked by their specific antagonists, atropine (Inoue *et al.*, 1983) and propranolol (Shirakawa *et al.*, 1983). In the frog, bombesin is also a potent stimulus of pepsinogen secretion (Shirakawa *et al.*, 1983). Ca^{++} removal partly or completely inhibits most stimuli (Koelz *et al.*, 1982; Inoue *et al.*, 1983), and dibutyryl cAMP stimulates in all preparations. All stimuli increased cAMP production in the presence of the phosphodiesterase inhibitor IBMX (Shirakawa *et al.*, 1983; Inoue *et al.*, 1983). The combined evidence suggests that both Ca^{++} and cAMP are involved in stimulation by all active stimuli—CCK in rabbit and guinea-pig, cholinergic and adrenergic in mammals and the frog, and bombesin in the frog. From the handful of papers on isolated peptic glands reported so far, it has not been possible to ascribe either/or specificity of second messengers, i.e. either Ca^{++} or cAMP, to any one of the known stimuli of pepsinogen secretion. Correlation of *in vitro* data with data from the intact animal agrees with respect to cholinergic stimulation, but disagrees regarding secretin, histamine and gas-

trin, which stimulated *in vivo*, but not *in vitro*. In isolated vectorially oriented peptic cells from the dog, histamine was found to stimulate electrolyte transport, but not pepsinogen secretion (Ayalon *et al.*, 1982).

Physiology

Pepsinogen secretion in intact animals and man. In the intact stomach of the mammal, the peptic cells are co-mingled with parietal cells even to the extent of forming tight junctions. Though under many, if not most, conditions, peptic and parietal cells function in concert, they are capable of independent function (Hirschowitz, 1967a, b). Thus, there are well defined circumstances where peptic cells are actively stimulated while parietal cells are inhibited (and *vice versa*); thus insulin inhibition of acid secretion in the dog does not affect the simultaneous hypoglycaemic-vagal stimulation of the peptic cells whilst secretin *in vivo* reduces acid, while stimulating pepsin in both man and dog and both acid and pepsin in the chicken (Burhol, 1982). In the opposite condition, administration of histamine to dogs and cats will strongly stimulate acid secretion yet inhibit pepsin secretion. Both actions are mediated via H_2 receptors (Hirschowitz and Hutchison, 1977a; Hirschowitz, Rentsch and Molina, 1981). Atropine added to histamine further accentuates the discrepancy, while vagal or cholinergic stimulation during histamine infusion will stimulate pepsin secretion without necessarily further affecting acid secretion (Hirschowitz, 1967a, b). In birds, such as the chicken, in which acid and pepsin are secreted by one cell, it was also possible to separate responses of the two cell products with some stimuli (Burhol, 1982), suggesting different messenger pathways specific to each cell product.

There are clear species differences in the response of peptic and parietal cells to stimuli. Thus, in man histamine stimulates acid and pepsin equally, and the specific H_2 receptor antagonists equally reverse the stimulation of both. Gastrin also stimulates both well. While the vagus stimulates both acid and pepsin via muscarinic pathways, only the acid secretion is inhibited by H_2 antagonists. Since H_2 antagonists inhibit acid secretion resulting from all stimuli, but pepsin only when stimulated by histamine, it seems clear that the peptic cell, unlike the parietal cell, neither has an absolute dependence upon histamine nor is approached by all stimuli via an H_2 histamine pathway. The stomachs of humans respond poorly to the acetylcholine analogues, bethanechol, carbachol or metacholine, which are potent stimuli in dog and cat acting via muscarinic M-1 (high affinity for the novel antimuscarinic drug, pirenzepine (Hirschowitz, Fong and Molina, 1983) receptors. In dogs H_2 antagonists non-competitively inhibit acid secretion

only, leaving cholinergically stimulated pepsin secretion intact (Hirschowitz and Molina, 1983). Basal secretion of both acid and pepsin in man is cholinergic and inhibitable by very small doses of atropine (Hirschowitz, Molina and Ou Tim, 1984).

In dogs and cats, histamine stimulates pepsin secretion at very low doses via high affinity (low dose) H_2 receptors and dose-responsively inhibits pepsin secretion via low affinity (high dose) H_2 receptors (Hirschowitz and Hutchison, 1977a, b; Hirschowitz *et al.*, 1981). No such inhibition is seen in man. In the dog, gastrin stimulation of pepsinogen secretion is somewhat less potent than acid stimulation. In rats, pigs and monkeys, histamine stimulates pepsin secretion as in man.

One unexplained stimulus for pepsin secretion is luminal application of HCl (Bynum and Johnson, 1975). This phenomenon has been ascribed to an osmotic effect by one group (Puurunen, 1979) and to initiation of local cholinergic reflexes by another (Bynum and Johnson, 1975). A change in the luminal membrane of the peptic cell promoting fusion with granules is another possibility. However, under many conditions pepsin secretion may be very low in the presence of high concentrations of acid (Hirschowitz, 1967b).

Receptor-specific inhibitors. Specific inhibitors behave predictably—thus atropine blocks equally the acid and pepsin stimulated by cholinergic agonists. The actions of atropine also define both basal secretion in man (the dog and cat do not have basal secretion), and direct vagal stimulation of the fundus in all species as acting via muscarinic pathways (Hirschowitz *et al.*, 1983, 1984).

Likewise, histamine effects are specifically antagonized by histamine H_2 antagonists. The controls of acid and pepsin secretion in intact systems are less clear because of the cross-over effects of antagonists, e.g. H_2 receptor antagonism of gastrin or vagal/cholinergic stimulation (Hirschowitz and Molina, 1983), atropine inhibition of gastrin (Hirschowitz and Hutchison, 1977a, b) and, to a lesser extent, of histamine stimulation (Hirschowitz, Hutchison and Sachs, 1973).

Other inhibitors. Somatostatin inhibits both acid and pepsin, most potently when acting against cholinergic stimuli, less so against gastrin and hardly at all against histamine (Hirst *et al.*, 1982). Prostaglandin E_2 has the reverse order of potency (Mihas, Gibson and Hirschowitz, 1976). How these agents act or by what mechanism they are equally effective in the disparate cell types is unknown. Presumably, they act upon second messenger steps that both cell types have in common. From the pattern of antagonism one would expect that somatostatin acts on the Ca^{++} dependent pathways and prostaglandin E_2 on the cAMP pathways.

Combining data from intact systems with those from isolated tissues or cells, we may conclude that the peptic cell probably has receptors for acetylcholine in all species, including the frog. Histamine H_2 receptors mediate stimulation of pepsinogen secretion in man; both stimulation and inhibition in dogs and cats; neither in rabbit or frog. Gastrin, for which no good specific antagonist is available, stimulates peptic cells in man and dog, and is very sensitive to atropine (Hirschowitz and Hutchison, 1977a, b), but stimulates poorly in rabbits and not at all in frogs. Both histamine and gastrin are good stimuli of the mixed function cells of the chicken (Burhol and Hirschowitz, 1971; Burhol, 1982). CCK, however, is a weak stimulant in man, dogs and chickens, stronger in the rabbit, but inactive or nearly so in frogs.

Pathophysiology of pepsinogen

In duodenal ulcer (DU) patients as a group, under basal or stimulated conditions, pepsin output, like acid output, is on the average 1.5 to 2 times greater than in controls (Hirschowitz, 1984). DU males secrete more acid and pepsin per kg body weight than do DU females. The overlap between DU and controls amounts to perhaps 50% of DU and 85% of controls. There is no difference between patients with DU or Zollinger-Ellison syndrome and non-ulcer subjects in the relative ratios of acid to pepsin secretion (Hirschowitz, 1983; Aly and Emas, 1982), suggesting that the gastric hyperplasia seen in many, but not all, DU equally affects all cells of the gastric mucosa. It has been reported that pepsin secretion is higher in active than inactive or healed DU (Elder and Smith, 1975; Achord, 1981). This could not be confirmed (Hirschowitz, 1984). The attempts to find consistent or useful patterns of electrophoretically separable pepsins in gastric juice of patients with gastric or duodenal ulcer, gastritis or cancer (Elder and Smith, 1975; Samloff, 1983; Taylor, 1970; Walker and Taylor, 1980; Walt, Roberts and Taylor, 1979) have not yielded much firm data. Little of practical clinical value has emerged from these studies. Treatment of DU with pepsin antagonists has not been found useful, especially in the era of H_2 antagonists.

In gastric ulcer, pepsin secretion, like acid secretion, is the same as in controls. After vagotomy for DU, those without ulcer secrete in the normal range, but those with recurrent ulcer are closer to unoperated DU, probably because of incomplete or inadequate surgery. In atrophic gastritis, pepsin and acid secretion both decline to the point of virtual or complete absence, as in pernicious anaemia.

Much has been written about the measurement of urinary or serum pepsinogen. In the 1940s and 1950s

these measurements involved total proteolytic activity. No direct relationship could be established between gastric pepsin secretion and either serum or urine pepsinogen. In young army recruits, those with a high serum pepsinogen had a much higher later incidence of DU than those with normal values (Mirsky *et al.*, 1948), though the incidence was not high enough to be useful as a general marker. As a group, patients with duodenal ulcer have significantly higher levels of serum and urine pepsinogen than controls; 60% of DU had serum pepsinogen greater than controls (Hirschowitz, 1953, 1955). Stimulation and inhibition of gastric secretion was not reflected by corresponding urine or serum levels (Hirschowitz, 1955). In pernicious anaemia or after total gastrectomy, serum and urinary pepsinogen levels are extremely low but not entirely absent, indicating other sources of pepsinogen, from prostate and leucocytes. In partially gastrectomized DU without recurrent ulcer, levels were as low as in normal, while those with recurrent ulcer had higher levels. Thus, in all respects, urine and serum pepsinogen levels were of no greater clinical or diagnostic value than gastric analysis and fell out of favour, especially with the rapid development of universal upper GI fiberoptic endoscopy after 1960.

With the development of radioimmunoassay for PGI and II, interest has again revived in the possible clinical usefulness of measurements of serum pepsinogens (Samloff, 1983). The correlation between PGI and total proteolytic activity in the serum is good and, in fact, would predict that the pattern of distribution of PGI values would be very similar to that found with chemical serum pepsinogen measurements 30 years ago (Hirschowitz, 1955). Such was the case in a large study involving over 900 subjects (Samloff, Liebman and Panitch, 1975), and the diagnostic usefulness in individual cases is no greater now than it was then. However, several interesting findings have emerged from these studies.

As mentioned earlier, urinary pepsinogen is all PGI except in premature infants and in cases of renal failure with proteinuria, suggesting that PGI and II are both filtered, but that PGII is reabsorbed preferentially over PGI in the healthy kidney. In most persons, PGI in the urine comprises pepsinogens electrophoretically identified as Pg 1-5. However, in some subjects, Pg 5 is missing. This trait, possibly linked to HL-A loci (Weitkamp, Towner and May, 1975), affects 14% of non-ulcer whites as an autosomal recessive, and affects more than 14% of blacks, but is not found in those of East Asian descent (Samloff, 1983).

Serum pepsinogen comprises six times more PGI than PGII. The relative abundance of PGII is not surprising since PGII is not excreted in the urine. About 2/3 of DU have serum PGI values above

control (Samloff *et al.*, 1975)—the same proportion as for total pepsinogen (Hirschowitz, 1955). In a few Zollinger-Ellison cases even higher levels were seen (Samloff *et al.*, 1975). Recurrent ulcers have more PGI than do successfully operated DU patients (Samloff *et al.*, 1975), again confirming earlier reports based on total proteolytic activity (Hirschowitz, 1955). In cases of fundic atrophy, PGI tends to disappear, but, since the antrum remains intact in most pernicious anaemia patients, PGII persists undiminished (Samloff, 1982). There are, however, more direct ways of diagnosing pernicious anaemia.

In two families of patients with DU and elevated serum PGI, 50% of first degree relatives with elevated PGI, distributed as an autosomal dominant, were liable to have DU (Rotter *et al.*, 1979), whereas those with normal serum PGI were free of DU. An elevated PGI might thus serve as a marker for DU, though no correlation with any haplotypes, blood types or other possible markers has been so far clearly established (Walt *et al.*, 1979; Weitkamp *et al.*, 1975).

What, then, is the potential value of measuring PGI and II in blood and urine? For diagnosis of gastric or duodenal disease, the value of serum PGI measurement appears limited, especially since the test involves an expensive radioimmunoassay, unlikely to be performed regularly in any clinical laboratory. The same is true of pernicious anaemia and Zollinger-Ellison syndrome, for which better and more specific tests are available. Similarly for the diagnosis of duodenal, gastric or recurrent postoperative peptic ulcer, and of gastric cancer or gastritis, fiberoptic endoscopy, though more expensive, is easier and definitive. For population screening, perhaps for closely defined genetic studies, measurement of PGs and variants in blood and urine may prove useful in a research context. Certainly measuring PGI is not a shortcut to studying gastric secretion directly.

Postscript

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