The Enterohormones

CURRENT STATUS AND REVIEW

A. I. VINIK

SUMMARY

In this review, the origin of endocrinology has been traced to the discovery of the first hormone, secretin, a gut hormone, by Bayliss and Starling 70 years ago. Since then gastro-enterological endocrinology has flourished with the discovery of a host of new hormones, including glucagon, enteroglucagon, gastrin, cholecystokinin-pancreozymin (CCK-PZ), gastro-intestinal inhibitory peptide (GIP), vaso-active intestinal peptide (VIP), motilin, and many others are awaiting discovery.

There is extensive overlap in the biological and immunological activity of these hormones which may be related to similarities in primary structure, a common ancestral molecular origin or relative non-specificity of the receptor sites in various target organs.

Administered gut hormones have proved useful in the diagnosis of many endocrine and non-endocrine disorders, and provide scope for the medical management of conditions hitherto considered to be primarily surgical.

Measurements of circulating levels have given us a deeper understanding of physiological and pathophysiological processes, and in many instances are the simplest and most rapid means of diagnosing certain disease processes.

The review was intended to assist the busy practitioner to keep abreast of a rapidly-advancing field where new ideas and concepts appear at such a breathtaking rate that only the individual intimately concerned can keep pace. The author hopes to have at least achieved this objective.

S. Afr. Med. J., **48**, 359 (1974).

HISTORICAL

'It was a great afternoon', according to Sir C. J. Martin.[1] In the laboratory at University College he had watched Bayliss and Starling denervate the jejunal loop of an anaesthetised dog and put a small amount of weak hydrochloric acid into its colon. When pancreatic juice flowed, Starling realised 'it must be a chemical reflex'. A great afternoon it certainly was, for it marked the start of a new biological discipline, endocrinology.[2]

Endocrinology had its birth with a gut hormone. Following a rather long silent period, recent years have seen a veritable explosion in the area of gut hormones which will be reviewed.

Department of Medicine, University of Cape Town
A. I. VINIK

After 14 years of work Mutt and Jorpes,[3] in 1966, described the molecular structure of the hormone and in the same year Bodanszky *et al.*[4] synthesised secretin. In 1905 Edkins[5] proposed that a substance may be separated from cells of the mucous membrane which, when passing into blood or lymph, later stimulates the secretory cells of the stomach to functional activity. It was not until 1938 that Komarov[6] distinguished this material from histamine and termed it gastrin. In 1942 Uvnäs[7] demonstrated that vagal impulse released gastrin, and the role of gastrin in gastric acid secretion was firmly established. The characterisation and chemical structure of gastrin in 1964 by Gregory and colleagues[8] opened the modern era of the study of gastrin.

Fifty years ago Murlin *et al.*[9] discovered a hyperglycaemic contaminant of partially purified insulin. His observations were soon confirmed.[10] This hyperglycaemic factor was termed glucagon and it was only in 1956 that Bromer *et al.*[11] finally elucidated the structure of this molecule. This was soon followed by the synthesis of this hormone by Wünsch and Weinges.[12]

Cholecystokinin followed in 1928 and pancreozymin was isolated by Harper and Raper[13] in 1943. Cholecystokinin and pancreozymin (CCK-PZ) were shown to be one and the same hormone by Jorpes[14] in 1968, and were synthesised by Ondetti *et al.*[15] in the same year. Sutherland and De Duve[16] in 1948 found hyperglycaemic activity of extracts of small intestine and postulated the existence of a hormone akin to pancreatic glucagon. Unger *et al.*[17], as recently as 1968, established the secretion of gut glucagon-like material into the portal circulation of dogs, but as yet the nature and structure of these moleclues have not been identified. More recently, in this decade, further hormones have been added to this list, including GIP (gastro-intestinal inhibitory peptide, VIP vaso-active intestinal polypeptide), and motilin.

The biological actions of gastrin and secretin have been reviewed[2,18] and only pertinent aspects will be dealt with here.

OVERLAP IN EXOCRINE ACTIONS

Gastrin increases gastric acid secretion as its primary action and CCK accomplishes this as well. Similarly, CCK increase gall bladder contraction as its primary action and elicits an enzyme-rich fluid from the pancreas, effects shared by gastrin albeit in the case of the gall bladder, at a pharmacological dose. Furthermore, for pancreatic secretion of both bicarbonate and enzymes, gastrin augments CCK-PZ while the two hormones competitively inhibit each other with regard to hydrogen ion secretion by the stomach.

The molecular similarity between glucagon and secretin is also reflected in their functional similarity; both molecules inhibit gastric acid secretion and gastric motility. However, while secretin stimulates gastric pepsin secretion in man, the effect of glucagon is unclear. Glucagon has no effect on the basal pepsin production but inhibits histamine-stimulated release of pepsin. Glucagon and secretin are capable of enhancing the action, as seen in increased bile flow and output of sodium chloride and bicarbonate when the two hormones are administered together. Both hormones stimulate secretion of Brunner's glands in dogs and reduce the motility of intestine in man. In addition, the hormones release insulin from the pancreas and cause glycolysis in isolated fat cells. On the other hand, although glucagon does not alter basal pancreatic enzymes and bicarbonate secretion, it is capable of markedly inhibiting secretin-induced secretion although, somewhat surprisingly, the output of enzymes falls more than that of bicarbonate.[2]

If one compares the action of secretin and glucagon to that of gastrin and CCK, one again notices overlap in action between the two sets of hormones and again it may be seen that there are examples of competitive inhibition and competitive augmentation. Thus, secretin alone has no effect on gall bladder contraction but augments the action of CCK and non-competitively inhibits CCK or gastrin-stimulated acid secretion and shows non-competitive augmentation with gastrin or CCK on pancreatic bicarbonate and enzyme secretion.

OVERLAP IN ENDOCRINE ACTIONS

The diabetologists' and endocrinologists' interest in gut hormones dates to the observations in 1902 by Moore *et al.*[19] that feeding acid alcohol duodenal extracts lowered blood glucose in diabetic dogs. In 1954 Scow and Cornfield[20] found that glucose was removed more rapidly from the blood of rats when the dose was administered orally, than when injected intravenously. In 1964 McIntyre *et al.*[21] and Elrich *et al.*[22] attributed the more rapid removal of oral glucose to the augmented insulin secretion seen after the oral dose. This enhancement of insulin release was not abolished by portacaval anastomosis,[23] suggesting that the higher levels of insulin and enhanced glucose tolerance following absorption of glucose from the gut were due to an intestinal factor, possibly a hormone, and thus confirming the earlier observations by La Barre and Shill[24] who showed that the intravenous injection of a duodeno-jejunal extract into dogs, caused hypoglycaemia mediated by the pancreas. La Barre suggested the name 'incretin' for this intestinal factor, and as yet the nature of this material has not been resolved. Several of the hormones released from the intestinal mucosa are capable of stimulating insulin release. The main candidates have been secretin, CCK, gut glucagon and gastrin, while GIP has now entered this arena.

The rise in circulating gut glucagon-like material, after the ingestion of oral glucose, has been demonstrated by Unger *et al.*[17] Gut glucagon has been shown to promote insulin release from the pancreas and could therefore be the material referred to as incretin. However, the physiological significance of gut glucagon secretion in relation to insulin output is uncertain.[25]

Secretin is another contender for this role. Ingestion of glucose causes a rapid and large increase in circulating secretin-like material[26] and, as referred to earlier, secretin causes a marked increase in insulin release from the pancreas.[27-29] Furthermore, secretin potentiates the glucose or amino acid-stimulated insulin secretion.[30,31] However, the physiological relevance of these observations still remains in doubt, since instillation of hydrochloric acid into the duodenum, which elicits a rise in circulating secretin, does not consistently increase insulin secretion.[29,31,32] Finally, it has been suggested that the release of insulin by the pancreas after secretin stimulation requires the integrity of the exocrine pancreas.[33]

The third candidate for this function, CCK-PZ, appears to release insulin independently of the integrity of the exocrine pancreas. In addition CCK-PZ is the only gastro-intestinal hormone that has been shown to stimulate glucagon release from the pancreas,[27] thus CCK-PZ could act as a stimulus for insulin secretion by a dual mechanism, firstly by direct stimulation and secondly by the release of pancreatic glucagon. More recently, however, highly purified CCK-PZ has been shown to be devoid of insulogenic activity — which could be attributed to the contaminating GIP content.

Gastrin has also been shown to release insulin from the pancreas directly, but only in pharmacological amounts. Furthermore, we have presented evidence militating against a physiological role for gastrin in initiating insulin secretion. Nevertheless, it is clear that gut glucagon, secretin, CCK-PZ, GIP and probably gastrin, may all fulfil the role of a hypothetical hormone 'incretin' and act as signals for the release of insulin on the arrival of food in the gastro-intestinal tract. Such an action would fulfil a physiological need and anticipate the presentation of food substrate into the circulation, and so minimise large unphysiological fluctuation in plasma substrate levels. Since these hormones not only release insulin, but interact with each other — for example gastrin serves as a direct stimulus to the release of secretin and, vice versa, secretin may inhibit gastrin release — it is clear that this role is subserved by more than one hormone and that 'incretin' is not a hormone but rather a concept involving multiple hormones interacting with each other upon insulin secretion from the pancreas.

Grossman[34] has postulated from the above findings that gastrin, CCK, secretin, and probably glucagon, act on one receptor. The receptor is said to have two interacting sites, one with an affinity for the chemically related gastrin and CCK, and another for secretin and the similar glucagon. His hypothesis predicts that all target organs that react with one of these hormones will react to the other two, and predictably glucagon as well. Simultaneous action of the two hormones leads to competitive or non-competitive augmentation or inhibition, depending upon whether the hormones are acting on the same or different interaction sites, and whether the hormones acting on the receptor are stimulatory or inhibitory. In other words, if both hormones have a stimulatory action at a particular site, then in concert they will non-competitively augment each other. If one

hormone has an inhibitory action, and the other a stimulatory action at a particular site, they will then competitively antagonise each other's action. It appears that glucagon will act at these receptor sites in very much the same way. However, one difference which emerges is the fact that glucagon has glycogenolytic and gluconeogenic properties which are not shared by the other gastrointestinal hormones, although even this is open to some doubt.[35]

PRIMARY STRUCTURAL SIMILARITIES

The question which arises is why these hormones have such tremendous overlap in both their endocrine and exocrine functions.

TABLE I

Glucagon (mol. wt 3 485)
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-*Asp-Ser*-Arg-*Arg*-Ala-*Gln*-Asp-Phe-Val-*Gln*-Try-*Leu*-Met-Asn-Thr.

Secretin (mol. wt 3 055)
His-Ser-Asp-*Gly-Thr-Phe-Thr-Ser*-Glu-Leu-*Ser*-Arg-Leu-Arg-*Asp-Ser*-Ala-*Arg*-Leu-*Gln*-Arg-Leu-Leu-*Gln*-Gly-*Leu*-Val-NH_2.

Enterogastrone (GIP) (mol. wt 5 105)
Tyr-Ala-Glu-*Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser*-Ile-Ala-Met-*Asp*-Lys-Il-*Arg*-Gln-*Gln-Asp-Phe-Val-Asn-Try-Leu-Leu*-Ala-Gln-Gln-Lys-Gly-Lys-Lys-Ser-Asp-Tryp-Lys-*His*-Asn-*Ile-Thre*-Gln-NH_2

Cholecystokinin-pancreozymin (CCK-PZ) (mol. wt 3 727)
Lys-(Ala,Gly,Pro,Ser)-Arg-Val-(Ile,Met,Ser)-Lys,Asn-(Asn,Gln,His,Leu,Leu,Pro,Ser,Ser)-Arg-Ileu-(Asp,Ser)-Arg-*Asp-Tyr-Met-Gly-Try-Met-Asp-Phe-NH_2*
$S^{\uparrow}O_3$

Synthet. octapeptide from CCK-PZ (mol wt 1 143)
Asp-Tyr-Met-Gly-Try-Met-Asp-Phe-NH_2
$S^{\uparrow}O_3$

Gastrin I (human) (mol. wt 2 200)
Pyr-Gly-Pro-Try-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-*Gly-Tyr-Met-Asp-Phe-NH_2*

Gastrin II (human) (mol. wt 2 280)
Pyr-Gly-Pro-Try-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-*Gly-Try-Met-Asp-Phe-NH_2* $S^{\uparrow}O_3$

Gastrin pentapeptide (ICI) (mol. wt 653)
Gly-Try-Met-Asp-Phe-NH_2

Caerulein (mol. wt 1 258)
Pyr-Gln-*Asp-Tyr*-Thr-Gly-Try-Met-Asp-Phe-NH_2
$S^{\uparrow}O_3$

Examination of the primary structure of these hormones (Table I) provides us with a clue. Comparing the C terminus of the peptide of cholecystokinin-pancreozymin with that of human gastrin, one notes an identical pentapeptide in the two molecules. It is of interest that this pentapeptide has also been found to occur in a decapeptide caerulein isolated by Erspamer *et al.*[36] from the skin of the Australian frog *Hyla caerulea*. Furthermore, this small pentapeptide, pentagastrin, has all the biological properties of human gastrin, although at a higher molar concentration, and a comparison of the homology of secretin and glucagon reveals that 14 of the 27 amino acids in secretin are identical in position to those of the 29 amino acids of glucagon. Comparing Brown's enterogastrone, which is probably GIP, with glucagon and secretin, one is again struck by the tremendous overlap in primary structure of the three hormones. It is apparent that gastrin and CCK, with their shared primary structure, have a broad spectrum of action on many different glands and muscles and act essentially on the same targets with only a few exceptions.

ORIGIN, ERA AND SPECIES OF GUT HORMONES

Is this complex interaction between these hormones a question of chance, or is there some anatomical, embryological or other reason? Gastrin has been isolated from the gastric antral mucosa, and CCK-PZ, secretin and gut glucagon from the small intestinal mucosa. Furthermore, these hormones, or cells producing these hormones, have been found in the pancreas as well. The endocrine glands are usually described as being derived from all three germinal layers: firstly, ectodermal derivatives including the pituitary and adrenal medulla; secondly, endodermal or foregut derivatives including the parathyroid, thyroid, pancreatic islets and the ultimobranchial body; and thirdly, those from the nephrogenic ridge, the ovary, testis and adrenal cortex which are thought to be mesodermal in origin. The developmental, histological and biochemical similarities of the peptide-secreting endocrine glands, the frequent occurrence of multiple endocrine tumours of these glands, and the frequent production of peptide hormones by non-endocrine foregut derivatives, suggest that the ectodermal and endodermal endocrine glands are related through a common stem cell precursor in the foregut mucosa.

These cells are probably neuro-ectodermal in origin and migrate into the primitive alimentary tract in which they form the enterochromaffin system and are carried, with the buds of the various endocrine glands, to their resting places in the anterior pituitary, thyroid, parathyroid, islets of Langerhans, ultimobranchial body and thymus. They also form the chromaffin system, the adrenal medulla and the ganglia of the autonomic nervous system and the chemoreceptor system which are present in the hypothalamus and give rise to the posterior pituitary hormones.[37]

Employing a method which depends on the production from an exogenous percursor of an amine which is stored in specific granules and which is convertible by treatment with hot formaldehyde vapour into a fluorescent derivative, Pearse and Polak[38] have demonstrated the neuro-ectodermal origin of these endocrine-secreting cells in the gut and pancreas. These cells have been referred as the APUD-FIF series and have been found in the gut and in the pancreas. Included among these are the C cells of the thyroid gland known to secrete thyrocalcitonin. For instance the C cells of the ultimobranchial body ultimately produce thyrocalcitonin while the pyloric G cells produce gastrin. It is, however, less easy to see how cells of a single type, sharing the same

environment, are modified to produce a number of different hormones, even as in the case indicated above, their primary structures contain identical amino acid sequences. Nevertheless, to quote Polak,[38] 'the APUD-FIF cells appear to be brothers under the skin and it is perhaps not surprising that they appear to recognise and to respond to each others products'.

If one examines the origin, era and species of these hormones, further light can be shed on this matter. Secretin, for example, has been found in the intestine of amphibia and elasmobranchs suggesting a mid-palaeozoic origin approximately 300 million years ago. It has also been found in birds, reptiles and teleost fish and in all mammals studied.[39] Similarly, gut glucagon has been isolated from a number of cold-blooded vertebrate species, including the eel, frog and tortoise, and from lower invertebrate species,[40] although in the latter the exact origin of the material remains obscure since the whole animals were extracted. Pearse and Polak[38] identified cells in the gastro-intestinal mucosa excluding the pylorus and duodenum, and which were most numerous in the fundus and the mid- and terminal jejunum, which they termed enteroglucagon cells (EG cells).

Thus there is phylogenetic, embryological, morphological, pathophysiological and biochemical evidence in terms of primary structural similarity, of a common origin of these hormones. This renders it somewhat easier to understand the complex nature of the interaction between these hormones and their shared functional activity. What remains a little more difficult to comprehend is what their original function was, and how they become individually regulated in the advanced *Homo sapiens*.

With regard to the first, I propose that these hormones arose from a common ancestor molecule, say some 300 million years ago and subserved a function entirely unrelated to their present function. As an example we have parathyroid hormone which is present in invertebrates and therefore cannot be responsible for regulation of calcium homeostasis in bone, and it is clear that at some stage it was a hormone primarily concerned with regulation of acid-base balance. These hormones, we know, are markedly elevated in hyperosmolar syndromes and are also responsible for the marked outpouring of fluid into the gastrointestinal tract. It is possible that at some stage they served a primary role of regulating acid-base and water and electrolyte metabolism, and with evolution have come to function in a more refined capacity. It seems that the gut represents a massive endocrine organ which anticipates the arrival of substrate and so activates each of the other endocrine glands in turn. For example, glucagon is known to stimulate pituitary growth hormone secretion, or alternatively thyrocalcitonin output from the C cells of the parathyroid, and thirdly insulin secretion from the pancreas. We once regarded the pituitary gland as the director of the endocrine orchestra and some schools have now suggested that the hypothalamus has replaced the pituitary gland in this capacity. I suggest that we should look at the gut as an endocrine organ which is the primary dictator in the sequence of events determined by endocrine activity.

The second proposal, or the second problem, poses some difficulty. There are three possibilities which come to mind, firstly that local nervous and humoral factors determine the release of a specific hormone at a specific site; secondly that only parts of the parent ancestral molecule are synthesised and released from a particular tissue which retains the capacity, under certain circumstances, to revert to its former nature and produce the parent molecule and related molecules; and thirdly that these cells are under the influence of some other regulatory glands, for example the pituitary. It is known, for example, that in acromegaly with over-secretion of growth hormone, the pancreas over-secretes glucagon and possibly gastrin, which suggests the presence of an entero-endocrine and pituitary-entero feedback system.

ADMINISTERED GASTRO-INTESTINAL HORMONES IN DIAGNOSIS

Gastrin is the preferred stimulant for routine gastric secretory testing because it produces the same maximal response as histamine or betazole but with almost none of the unpleasant side-effects. Since pentagastrin, the terminal pentapeptide of gastrin (ICI), is more readily available, it is usually used. It has all the actions of gastrin but is less potent.

Secretin is used in diagnostic pancreatic secretory tests and since no fraction of the molecule is biologically active, the whole molecule must be used. Pure porcine secretin as the natural product is employed, because synthetic secretin is in very short supply.

CCK - PZ is useful for contracting the gall bladder and demonstrating the biliary ducts during cholecystography. In theory CCK - PZ should be superior to the traditional fatty meal, because it does not depend on the vagaries of gastric emptying and the variable ability of the intestine to release CCK - PZ in response to fat. The minimal fragment of CCK with the biological actions of the whole molecule is the carboxyterminal heptapeptide-amide which contains the minimal fragment of gastrin. This minimal fragment is more potent than the whole molecule and has all the actions of CCK - PZ, as does the substance caerulein; CCK - PZ has also been used to test pancreatic function. When CCK - PZ and secretin are given together they markedly augment the enzyme-stimulating action of CCK - PZ, and conversely CCK - PZ, a primary stimulant of enzymes acting with secretin, markedly augments secretin bicarbonate-stimulating action, and when given together, they improve the diagnostic discrimination in clinical pancreatic secretory tests.

Glucagon, which is available as pure pancreatic glucagon, has been established as a test for virtually every endocrine dysfunction syndrome. Firstly, since it provides the release of catecholamines from the adrenal medulla it is used for the diagnosis of phaeochromocytoma, and secondly, it is a potent stimulant of the thyroid C cells and has been of use in the diagnosis of medullary carcinoma of the thyroid. Thirdly, it is a potent neoglucogenic and glycogenolytic hormone and is useful in the diagnosis of chronic liver disease. The pituitary is stimulated to release growth hormones and glucagon is used as a diagnostic test of pituitary insufficiency. Finally, glucagon is safer

than tolbutamide in eliciting insulin secretion from an insulinoma and has been used with some success in the diagnosis of this tumour.

THERAPEUTIC USES OF GUT HORMONES

Since secretin stimulates pancreatic production of highly alkaline juice and increased bicarbonate secretion from the liver, hepatic bile, Brunner's glands, and weakly inhibits gastric acid production and suppresses gastrin release, it has been proposed as a possible therapeutic measure for peptic ulceration, and duodenal ulcer. Certainly in rats, simultaneous administration of secretin prevents the hyperplasia of parietal cells that occur during long-term dosage with pentagastrin. It may be that when a long-acting synthetic analogue of secretin is available, it could cause hypoplasia of parietal cells and produce a medical gastrectomy.

CCK - PZ and related peptides are such powerful stimulants of propulsive motility in the large and small gut that they may be of considerable use in paralytic ileus. Caerulein also falls into this category. CCK - PZ and related peptides are also powerful relaxants of the sphincter of Oddi and one ought to give consideration to the use of this peptide in the treatment of biliary colic and of stones in the common duct after cholecystectomy.

Therapeutically, long-acting glucagon is valuable in the treatment of some hypoglycaemic disorders; especially when there is difficulty in administering glucose intravenously or by mouth, glucagon subcutaneously provides fairly prompt relief of the hypoglycaemia.

More recently Knight *et al.*[41] have proposed that in acute pancreatitis, glucagon is secreted, which in turn suppresses pancreatic exocrine function; this prevents the outpouring and release of inordinate amounts of enzymes responsible for the gross destruction seen in pancreatitis. When the serum glucagon level falls, haemorrhagic or necrotic pancreatitis sets in. They have suggested that this complication can be averted by continuous administration of glucagon. At present such a trial is underway in this hospital and we await with interest the results thereof.

There have been further suggestions that glucagon is causally related to the inevitable increase in tissue protein breakdown that follows severe injuries and major operations. It becomes theoretically possible that when glucagon analogues are available which compete with glucagon, or alternatively secretin, which is structurally similar, and which may competitively antagonise the action of glucagon in this respect, these will be of use in the prevention of the severe protein breakdown and tissue destruction which occurs in the postoperative or post-traumatic state.

It has been suggested on the basis of the ability of exogenous glucagon to reduce plasma cholesterol and triglyceride levels that this hormone may be of some use in the prophylaxis of myocardial infarction resulting from generalised atheroma. This hormone has also won some favour in the treatment of refractory congestive cardiac failure, since it increases the rate and force of contraction of the myocardium.[42]

CIRCULATING LEVELS IN DIAGNOSIS

The prime and already classic example of involvement of the gut hormones in the pathogenesis of disease is the Zollinger-Ellison syndrome with three cardinal features: fulminating peptic ulcer, massive secretion of acid by the stomach, and islet cell tumours of the pancreas which do not arise in the beta cells and do not secrete insulin.

Until recently the diagnosis of the Zollinger-Ellison syndrome has depended upon the demonstration of massive gastric hypersecretion. An overnight 12-hour gastric aspiration should yield more than 1 000 ml of fluid containing more than 100 mEq of acid. The basal acid secretion should be very high and approach the levels obtained after administering pentagastrin, so that little increase occurs on maximal stimulation. The clinching of the diagnosis is the finding of a high fasting level of serum gastrin, provided that pernicious anaemia has been excluded. Gastrin levels should also be measured in all patients who have severe ulcer symptoms, unexplained diarrhoea, or multiple endocrine abnormalities, since the Zollinger-Ellison syndrome has been reported as part of the MEA syndrome, including adenomata of the parathyroid, pituitary and carcinoid syndromes. We have measured gastrin levels in one patient with medullary carcinoma of the thyroid, and it would appear that these are elevated and hence would add yet another multiple endocrine abnormality syndrome.

Recently Polak *et al.*[43] divided patients with these syndromes into two groups on the basis of immunofluorescent, immunochemical and ultrastructural findings. In the first group, type I disease, the patient has a short history, very high levels of serum gastrin, profound hyperplasia of the gastrin-secreting G cells in the gastric antrum, and a normal pancreas. Patients with type II disease have longer histories, less extreme hypergastrinaemia, a normal population of antral G cells, but hyperplasia or frank tumour of the pancreatic islets. This has important implications in management because patients with type I disease should be cured with a lesser operation than total gastrectomy; in fact a patient has been reported where vagotomy and antrectomy abolished the symptoms and serum gastrin levels returned to normal within 2 months. It is also important to note in this context that we can now recognise a new type of gastric tumour arising from antral G cells which may mimic Zollinger-Ellison syndrome and require only resection of the secretory tumour of the stomach.[44]

Another syndrome in which an islet cell tumour of the pancreas has been implicated as a cause of diarrhoea, is the WDHA syndrome which represents watery diarrhoea, hypokalaemia with acidosis and achlorhydria. The diarrhoea may be so severe as to warrant the name pancreatic cholera, but since the term WDHA originated in this school, we prefer to adhere to that.[45] Elias *et al.*[46] have now produced evidence that the syndrome is caused by overproduction of an enterogastrone, namely GIP, and latterly revised this to include VIP. It seems, therefore, that the known syndromes associated with overproduction of intestinal hormones may only represent the tip of an iceberg, the remainder of which remains to be exposed. No doubt measurement of gut hormones in all cases of multiple endocrine adenomatosis, and in patients with strange

diarrhoeic syndromes will reveal further examples of over-secretion of gut hormones.

Serum gastrin measurements in patients with ordinary duodenal ulcer and gastric ulcer are less clear. One would expect duodenal ulcer patients to show raised levels of gastrin, and gastric ulcer patients to have depressed levels, but this is not the case. The explanation is simple: acid secretion reflexly inhibits the release of gastrin so that in duodenal ulcer patients the levels are frequently lower than those in gastric ulcers. An extension of this reflex arc is the fact that in patients with atrophic gastritis, or in pernicious anaemia patients who have achlorhydria, gastrin levels may be markedly elevated. This does not imply that gastrin is not implicated in the causation of duodenal ulcer for it appears that if one neutralises gastric acid secretion, the duodenal ulcer patient has the ability to hyper-respond and markedly elevate circulating gastrin concentration, while the gastric ulcer patient is secreting gastrin at the maximal rate. We propose to develop a bicarbonate tolerance test to neutralise gastric acid secretion and measure gastrin in the basal and stimulated states. Postoperatively, measurements of gastrin levels provide an excellent index of the effectiveness of gastrectomy, since levels fall to the undetectable zone. Also, when truncal vagotomy has been the procedure, and the antrum has been left intact, the basal gastrin level becomes markedly elevated, four to five times that of the normal untreated patient, and it is a useful marker of the effectiveness of the vagotomy.

Enteroglucagon measurements are useful in patients who present with reactive hypoglycaemia. There has been a problem in differentiating patients with reactive hypoglycaemia from those with islet cell tumour secreting insulin. It seems now that the reactive hypoglycaemic patient does not oversecrete insulin in response to, say, a meal or a glucose load, but rather oversecretes enteroglucagon. It has been suggested that the enteroglucagon competes with glucagon at the receptor sites in the liver and thus inhibits hepatic glycogenolysis and neoglucogenesis, resulting in decreased hepatic glucose output with a marked fall in blood sugar concentrations.[25]

In conclusion, I quote Professor Bank: 'Endocrinology which was born with a flourish in the gastro-intestinal tract with the discovery of the first hormone, secretin, has returned to roost, and the place of the gastro-intestinal endocrinologist is assured'.

REFERENCES

1. Martin, C. J. (1927): Brit. Med. J., **1**, 900.
2. Hubel, K. A. (1972): Gastroenterology, **62**, 318.
3. Mutt, V. and Jorpes, J. E. (1966): Abstract, 4th International Symposium on Chemistry of Natural Products, Stockolm.
4. Bodanszky, M., Ondetti, M. A. and Levine, S. T. (1966): Chem. Industr., **42**, 1757.
5. Edkins, J. S. (1905): Proc. Roy. Soc. B., **76**, 376.
6. Komarov, S. A. (1938): Proc. Soc. Exp. Biol. Med., **38**, 514.
7. Uvnäs, B. (1942): Acta physiol. scand., suppl. **4**, 1.
8. Gregory, H., Hardy, P. M., Jones, D. S., Kenner, G. W. and Shepherd, R. C. (1964): Nature (Lond.), **204**, 931.
9. Murlin, J. R., Cloth, H. O., Gibbs, C. B. F. and Stokes, A. M. (1923): J. Biol. Chem., **50**, 253.
10. Burger, M. and Kramer, H. (1930): Arch. Exp. Path. Pharm., **156**, 1.
11. Bromer, W. W., Sinn, L. G., Staub, A. and Behrens, O. K. (1956): J. Amer. Chem. Soc., **78**, 3858.
12. Wünsch, E. and Weinges, K. F. (1972): *Glucagon Molecular Physiology, Clinical and Therapeutic Implications*, p. 31. London: Pergamon Press.
13. Harper, A. A. and Raper, H. S. (1943): J. Physiol., **102**, 115.
14. Jorpes, J. E. (1968): Gastroenterology, **55**, 157.
15. Ondetti, M., Sheehan, J. T. and Bodansky, M. *in* Back, N., Martini, L. and Paoletti, R. eds. (1967): *Pharmacology and Hormonal Polypeptides*. New York: Plenum Press.
16. Sutherland, E. W. and De Duve, C. V. (1948): J. Biol. Chem., **175**, 663.
17. Unger, R. H., Ohneda, A., Valverde, J., Eisentraut, A. M. and Exton, J. (1968): J. Clin. Invest., **47**, 48.
18. Moshal, M. G., Broitman, S. A. and Zancheck, N. (1970): Amer. J. Clin. Nutr., **23**, 336.
19. Moore, B., Edie, E. S. and Abraham, J. H. (1902): Biochem. **J., 1**, 28.
20. Scow, R. D. and Cornfield, J. (1954): Amer. J. Physiol., **179**, 435.
21. McIntyre, N., Holdsworth, C. D. and Turner, D. S. (1964): Lancet, **2**, 20.
22. Elrich, H., Stimmler, L. and Hlad, C. J. (1964): J. Clin. Endocr., **24**, 1076.
23. McIntyre, N., Holdsworth, C. D. and Turner, D. S. (1965): *Ibid.*, **25**, 1317.
24. La Barre, J. and Still, E. W. (1930): Amer. J. Physiol., **91**, 649.
25. Rehfeld, J. F. and Heding, L. G. (1970): Brit. Med. J., **2**, 706.
26. Young, J. D., Lazarus, L. and Chisholm, D. J. (1968): J. Nucl. Med., **9**, 641.
27. Unger, R. H., Ketterer, H., Dupre, J. and Eisentraut, A. M. (1967): J. Clin. Invest., **46**, 630.
28. Deckert, T. (1968): Acta. endocr. (Kbh.), **59**, 150.
29. Chisholm, D. J., Young, J. D. and Lazarus, L. (1969): J. Clin. Invest., **48**, 1453.
30. Kraegen, E. W., Chisholm, D. J., Young, J. D. and Lazarus, L. (1970): *Ibid.*, **49**, 524.
31. Jarrett, R. G., Graver, H. J. and Cohen, N. N. (1969): Brit. Med. J., **4**, 598.
32. Mahler, R. J. and Weisberg, H. (1968): Lancet, **1**, 448.
33. Pfeiffer, E. F., Frank, M., Fufgänger, R., Goberna, R., Hinz, M. and Raptis, S. (1970): Nobel Symposium XVI, Stockholm.
34. Grossman, M. I. (1970): Lancet, **1**, 1088.
35. Youngs, G. (1972): Gut, **13**, 154.
36. Erspamer, V., Bertaccin, I., Bertogenni, G., De Carlo, G., Endean, R. and Impicciatore, M. (1967): Experientia (Basel), **23**, 702.
37. Weichert, R. F. (1970): Amer. J. Med., **49**, 232.
38. Pearse, A. G. E. and Polak, J. M. (1971): Gut, **12**, 783.
39. Grossman, M. I. (1958): Vitam. Horm., **16**, 179.
40. Assan, R., Tchobroutsky, G. and Rosselin G. (1969): Path. Biol., **17**, 747.
41. Knight, M., Condon, J. R. and Day, J. L. (1972): Clin. Sci., **43**, 597.
42. Editorial (1972): Lancet, **2**, 637.
43. Polak, J. M., Stagg, B. and Pearse, A. G. E. (1972): Gut, **13**, 501.
44. Editorial (1973): Brit. Med. J., **1**, 2.
45. Marks, I. N., Bank, S. and Louw, J. H. (1967): Gastroenterology, **52**, 695.
46. Elias, E., Polak, J. M., Bloom, S. R., Pearse, A. G. E., Welbourn, R. B., Booth, C. C., Kuzio, M. and Brown, J. C. (1973): Lancet, **2**, 791.