Pathophysiology of gastrin and secretin

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This paper will attempt to define the pathological roles of gastrin and secretin. It will deal predominantly with gastrin which now has an accepted role in some diseases, whereas the pathological role of secretin has still to emerge. Basic physiology and chemistry will only be described where these are considered to be relevant to the interpretation of the roles of these hormones in disease.

Gastrin

The history of gastrin began in 1905 when Edkins observed that an extract of gastric antral mucosa proved to have extraordinary potency in stimulating gastric acid secretion. Approximately 60 years later gastrin was isolated and characterised by Gregory and Tracy (1964). It is composed of a single peptide chain of 17 amino-acids (G17) with a molecular weight of 2100. Two forms of gastrin, I and II, were recognised initially, the only difference being that in II the tyrosyl residue in position 12 is sulphated. The synthesis of human gastrin was achieved by Morley in 1968.

The predominant biological activity of gastrin is that of increasing gastric acid production. Several other roles have been assigned to it including trophic effects on the stomach, effects on the exocrine pancreas, and on the enteroinsular axis, but they do not appear to play a role in pathological processes and will not be discussed further.

Gastrin is an antral hormone secreted by 'G cells' in the mid zone of the glands. However, smaller amounts of gastrin are present in the duodenum and jejunum and, in some species, there may be small amounts in the pancreas. Recently a substance which reacts with antigastrin antiserum has been detected in the central nervous system (Vanderhaeghen *et al.*, 1975). Immunochemical evidence so far suggests that the 'brain gastrin' consists of COOH terminal fragments of cholecystokinin (Dockray, 1976). The reason for the existence of gastrin-like peptides in the central nervous system is not known and so far they have not been shown to play a role in any pathological process in man.

THE NATURE OF GASTRIN

Like many other peptide hormones gastrin exists in multiple molecular forms. The reason why peptide hormones exist in multiple forms is still uncertain although in many instances, as in the case of pro-insulin and insulin, the relationship is likely to be that of a precursor and active hormone. Preparations of gastrin from gastrin-producing tumours, from normal tissues, and from circulating plasma have been characterised. It is fortunate that in several conditions blood levels of gastrin are very high, making investigation of circulating forms easier than in the case of some other peptide hormones. Although considerable progress in the characterisation of tissue gastrins has been achieved it is still not certain how closely these preparations resemble the circulating species.

Gregory and Tracy in 1975 isolated from both gastrinomas and hog antral mucosa two peptides containing 34 amino-acids. This gastrin has been referred to as G34 (big gastrin) in contrast with the heptadecapeptide G17 (small gastrin). Like G17 the two G34s differ only in the presence or absence of a sulphate on the tyrosyl residue. A 'mini-gastrin' has been isolated in small amounts from gastrinomas (Gregory and Tracy, 1975) and has been shown to have the amino-acid composition of the COOH terminal tetradecapeptide (G14). Another variant with the amino-acid composition of the 1-13 fragment of G17 has been isolated from antral mucosa (Gregory, 1974).

Components in the plasma which correspond with these different gastrins have been identified in some instances (Rehfeld and Stadil, 1973). Component III of plasma corresponds to G17, component II corresponds to G34, but component I of plasma, which elutes from Sephadex G50 between the void volume and G34, appears to have no tissue counterpart. An additional component in plasma, big big gastrin (BBG), which elutes from Sephadex G50 in the void volume, has been noted by Yalow and Berson (1972). It constitutes the major fraction of the immunoreactive gastrins extracted from fasting plasma but does not increase with feeding; it seems

likely to be an artefact which occurs on gel filtration of whole plasma as a result of non-specific binding of gastrin peptides to plasma proteins, a phenomenon observed frequently with other peptide hormones. The amino-acid sequences of some of the gastrins are shown in Fig. 1 and the relationships between tissue gastrins and plasma gastrins are illustrated in Table 1.

Plasma gastrin levels in fasting normal subjects do not correlate with basal acid secretion rates. This is perhaps not surprising as, in the fasting state, BBG, which is probably an artefact, constitutes the major part of the immunoreactive gastrin in plasma. This lack of correlation may be partly because of different proportions of G34 and G17, as G17 has a shorter half life than G34 in the circulation, though it is five times more potent than G34 in stimulating acid secretion (Walsh *et al.*, 1975).

Finally, it should be stated that the ability to detect multiple forms of a peptide hormone depends on the methods available. The considerable advances in the chemistry of gastrin have only been possible because of the use of multiple chemical techniques

by the groups of Gregory in Liverpool and Rehfeld in Copenhagen. In addition radioimmunoassay has made it possible to measure many samples simultaneously. However, there may be as yet unknown species of gastrin which cannot be detected by available antibodies, for example in large molecular species of gastrin the areas recognised by the antibodies may be hidden by other unknown and non-immunoreactive areas of the molecule. In addition tiny fragments of gastrin could be present in the circulation but unrecognised by any existing gastrin antibody.

METHODS OF INVESTIGATION

To assess the role of gastrin in health and disease the following techniques are required: radioimmunoassay, immunohistochemistry, electron microscopy of G cells, and physical and chemical methods for the characterisation of gastrin, including gel filtration and bioassay or assays using receptor site binding. Of these, radioimmunoassay has made the greatest contribution in recent years to the understanding of gastrin pathophysiology. Gastrin can be assayed in plasma, serum, or tissue extracts. It is relatively stable in blood, does not adhere to glassware, and can be assayed in plasma without preliminary extraction.

The gastrin radioimmunoassay in use in our department was described by Ardill (1973). The antibody 0098 was raised in rabbits against synthetic human gastrin I (Imperial Chemical Industries), containing amino-acids 2 to 17. The only other known gastrointestinal hormone with which this assay cross reacts is cholecystokinin, 1:10 000 by weight. The antibody also recognises gastrin G34 in equimolar amounts. The gastrin is iodinated by the chloramine-T method and the product purified by gel filtration. Equivalent amounts of plasma

Tissue gastrin	Equivalent form in plasma
—	Big big gastrin
—	Component I
Big gastrin (G34, non-sulphated and sulphated)	Component II
Gastrin (little gastrin) (G17)	Component III
I non-sulphated	
II sulphated	
Mini gastrin (a) G14 (residues 4 to 17 of G17)	Component IV
(b) G13 (residues 1 to 13 of G17)	

Table 1 Gastrins in human plasma and tissue

The plasma components still await full chemical identification, and only the probable tissue gastrin equivalent of the component is given. There is no tissue equivalent for 'big big gastrin' or component I.

Fig. 1 Amino-acid sequences of human gastrins. (a) Human big gastrin (G34) MW 3839. (b) Human heptadecapeptide, little gastrin (G17, R = H or SO₃H residues, 18-34 of G34) MW 2098. (c) Human minigastrin (G14, residues 21-34 of G34, 4-17 of G17). Pyr, pyroglutamyl; gastrin I, R = H; gastrin II, R = SO₃H.

adsorbed with charcoal (gastrin free) is added to the standards. The assay has a sensitivity of 5 ng/l but this sensitivity can be improved by a variety of manipulations including the use of disequilibrium conditions, reducing the concentrations of labelled hormone and antibody, and increasing the incubation volume and the amount of sample assayed. Greater sensitivity would also be achieved if a more sophisticated purification procedure were used for preparing the labelled hormone, and also a less harsh iodination technique. However, the assay is highly satisfactory for assay of gastrin in a variety of common clinical conditions.

The results obtained by radioimmunoassay of gastrin will vary according to the specificity of the antibody used. Antisera specific for different regions of the molecule will react differently with the various molecular forms of gastrin. Some antisera, like ours, will react with equimolar potency with components I to III, whereas an antiserum reacting exclusively with G17 (component III) has been described by Dockray and Taylor (1976). More sophisticated analysis of the different gastrins in plasma can be achieved by combinations of gel filtration, tryptic cleavage, and radioimmunoassay, as described by Rehfeld (1978). Clearly, there is the possibility of raising antibodies which will be highly specific for one or other species of gastrin, but before this can be achieved sufficient amounts of a highly purified preparation must be available.

Although radioimmunoassay of gastrin is essential in the investigation of pathological states the value of immunohistochemistry is less clear. The latter will make an important contribution to advances in knowledge of the role of gastrin in health and disease, but it generally contributes little to the assessment of clinical problems, mainly because of the difficulty of quantitative estimation. However, by means of it, the number of gastrin-secreting cells is shown to be grossly increased in achlorhydria, and it is also of considerable value in identifying gastrinomas, although a more sensitive and quantitative assessment is obtained by tissue extraction followed by radioimmunoassay of gastrin.

In clinical practice most states associated with abnormal gastrin secretion will be recognised by means of a robust and sensitive radioimmunoassay which shows equimolar reactivity with the different gastrin components in plasma and tissues. The use of the other techniques referred to above are only required occasionally, but their overall contribution to the future of research into gastrin in health and disease cannot be overemphasised.

PLASMA GASTRIN ASSAY IN DUODENAL ULCER
Recently, we assessed the value of a single fasting

blood gastrin estimation in the diagnosis of duodenal ulcer (DU). Between June 1975 and February 1977, which was before the introduction of H_2 -receptor blocking drugs, gastrin assays were performed in 223 patients diagnosed provisionally as DU or Zollinger-Ellison syndrome (ZES). In 192 patients additional information was available and the final diagnoses of these are shown in Table 2. Nine subjects (4.7%) had the ZES although some of them had had successful removal of the gastrinoma. A total of 147 patients had a duodenal ulcer but were thought not to have a gastrinoma; 12 of these were considered to have another reason for hypergastrinaemia, for example hyperparathyroidism, post-vagotomy, renal failure, and cimetidine therapy, leaving 135 patients (70.3%) with duodenal ulcer for further analysis.

We regard the upper limit of normal of plasma gastrin as 96 ng/l, with a mean value of 36 ng/l; these values are derived from 132 normal subjects. All the patients who were eventually proved to have the ZES syndrome had levels between 540 and 6500 ng/l. All but one of the patients who had had successful removal of the tumour had gastrin levels within the normal range, the exception having a slightly raised value of 105 ng/l.

The plasma gastrin levels in the control group, the DU group, and the patients with non-ulcer dyspepsia (NUD) are shown in Fig. 2. The patients with DU had a mean fasting level of 52.6 ng/l which is significantly raised compared with the control group ($P < 0.0005$). However, in patients with NUD the mean (44.7 ng/l) was not significantly different from the controls. Some of the blood samples from the DU patients may not have been taken under fasting conditions, but in 83 of them known certainly to have been fasting, the mean value was very similar to that of the group as a whole.

Of the 135 patients with duodenal ulcer unassociated with other conditions, 20 had levels above the

<i>Final diagnosis in 192 patients</i>		
<i>Diagnosis</i>	<i>No</i>	<i>%</i>
Duodenal ulcer (DU)	135	70.3
Pre- or postoperative ZES	9	4.7
DU with reason for hypergastrinaemia	12	6.2
Gastric ulcer	9	4.7
Gallstones	5	2.7
Hiatus hernia	1	0.5
Oesophageal reflux	1	0.5
Disseminated sclerosis	1	0.5
Non-ulcer dyspepsia	19	9.9

Table 2 Gastrin radioimmunoassay

Final diagnosis in 192 patients whose blood samples were referred for gastrin assay with the provisional diagnosis of 'DU' or 'ZES'.

Fig. 2 Plasma gastrin levels (mean + SEM) in control subjects (Cons), all patients with duodenal ulcer (DU), non-ulcer dyspepsia (NUD), and known fasting patients with duodenal ulcer (DU fast).

normal range. The results of another analysis performed in 13 of these are shown in Fig. 3. They were almost all lower than the first estimation, but several remained above the normal range. The 20 DU subjects with hypergastrinaemia were carefully analysed in order to discover whether they could form a separate group from the duodenal ulcer subjects with normal plasma gastrin levels. Basal acid output and maximal acid output after penta-gastrin were 3.09 and 23.81 mmol/h, respectively, which were less than the corresponding values of 5.70 and 30.78 for the DU group as a whole. Three subjects, however, did have pyloric stenosis and there were three children aged 8, 10, and 13 years, one of whom had a jejunal ulcer. In some of these subjects other tests were performed including antral biopsy, with radioimmunoassay of gastrin in an antral extract, immunohistochemical assessment of G cells, and provocative tests for gastrin release. However, no evidence was adduced that any of these subjects differed from the other DU subjects.

Our data showing that basal plasma gastrin is raised in patients with duodenal ulcer differ from those of most other authors, who report normal levels (Walsh and Grossman, 1973), although higher levels in the DU group than in a control population have been reported after a protein meal (McGuigan and Trudeau, 1973). Raised levels in patients with duodenal ulcer were reported by Byrnes *et al.* (1970), but their assay and normal range differ greatly from ours.

Although the mean plasma gastrin level in the duodenal ulcer group is significantly higher than in the controls, the assay is nevertheless not useful diagnostically, as in only 20 of the DU group was the level above the normal range. It is concluded that plasma gastrin estimation in patients with

Fig. 3 Difference between gastrin levels in 2 samples of blood from 20 patients with DU found to have high levels in the first sample in the absence of known causes of hypergastrinaemia (such as gastrinoma, renal failure, etc). The range for control subjects (Cons) is also shown.

duodenal ulcer is only of value in identifying the patients who have the Zollinger-Ellison syndrome.

There is no evidence that gastrin plays an important role in the pathogenesis of gastric ulcer. Many patients with gastric ulcer have hypochlorhydria which could account for a modest rise of plasma gastrin in some patients (Trudeau and McGuigan, 1971). However, some patients with gastric ulcer have antral gastritis and this might impair the release of gastrin.

HYPERGASTRINAEMIA

The usual causes of hypergastrinaemia are shown in Table 3, and most of them will be easily identified. The commonest reason for hypergastrinaemia in our experience is achlorhydria, hypergastrinaemia being presumably the result of the lack of the normal feedback inhibition of acid on gastrin release (Fig. 4). There is usually a massive rise of plasma gastrin in achlorhydria, the highest levels occurring in pernicious anaemia. The cause of the hypergastrinaemia can easily be confirmed by estimating the

Gastrinoma
Achlorhydria
Renal failure
Antral G cell hyperplasia
Vagotomy
Retained isolated antrum
Short gut syndrome
Cimetidine therapy

Table 3 Causes of hypergastrinaemia

Fig. 4 Fasting plasma gastrin levels in controls and in patients with pernicious anaemia (PA) and achlorhydria without anaemia.

gastric acidity or by showing circulating antibodies to the parietal cells, and there is usually no difficulty in distinguishing gastrinoma from achlorhydria.

Basal plasma gastrin levels and those after stimulation by food are increased by H₂-receptor antagonist therapy (Buchanan *et al.*, 1978). The importance of this hypergastrinaemia in long term cimetidine therapy is unknown but it raises the possibility of an increase in the parietal cell mass. It is clearly important when assessing a high plasma gastrin level and acid secreting status in a patient with duodenal ulcer to know whether the patient is taking cimetidine, which may have to be withdrawn for an accurate assessment to be made.

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)
Patients with a gastrinoma usually have severe progressive ulcer disease with multiple ulcers in atypical sites (Isenberg *et al.*, 1973). The history

is short, and often there are numerous complications including pyloric stenosis and perforation; frequently several operations have been performed before the correct diagnosis has been made. However, the clinical picture is not so distinctive as to make the diagnosis easy. Indeed the diagnosis is usually made by laparotomy, but if the correct diagnostic approach is adopted the surgeon will not find himself unexpectedly confronted with a tumour at laparotomy.

In addition to radiological investigations, the two laboratory procedures which are crucial in the diagnosis of gastrinoma are the assessment of basal gastric acid secretion (normally up to 15 mmol/h) and the fasting plasma gastrin level. We have always found plasma gastrin levels to be clearly above the normal range in patients with gastrinoma and regard further stimulatory tests of gastrin release, such as a protein meal, intravenous secretin, glucagon, or calcium (Basso and Passaro, 1970; Hansky *et al.*, 1971; Creutzfeldt *et al.*, 1975), as generally unnecessary. However, they may occasionally be useful when the rise of plasma gastrin is not as great as expected in gastrinoma. It is said that in patients with gastrinomas gastrin levels rise after the intravenous stimuli, whereas in normal subjects they do not.

The question arises of whether plasma gastrin should be measured in every patient who has peptic ulceration. The radioimmunoassay of plasma gastrin is easy to perform and we believe that one technician could easily cope with a single blood sample from every patient with peptic ulceration in a population of 2 million, and that this would result in early diagnosis of gastrinoma and a considerable decline in the morbidity and mortality. A considerable proportion of patients with gastrinoma have multiple endocrine adenomatosis (4 of 11 seen in this department in 8 years) and it is therefore important to screen these patients for other endocrine tumours. The estimation of plasma pancreatic peptide (page 43) may also be a useful adjunct in diagnosis. The treatment of gastrinoma is discussed elsewhere by Professor Welbourn (page 85).

ANTRAL G CELL HYPERPLASIA
Cowley *et al.* (1973) and Ganguli *et al.* (1974) described the syndrome of hyperplasia of the antral gastrin-secreting cells in peptic ulcer disease. It was suggested that there was a separate entity of patients with peptic ulcer and hypersecretion of acid who did not have a gastrinoma, but who had high fasting plasma gastrin levels and a further increase after a protein meal. Such patients had increased numbers of G cells in the antrum. A new classification of the ZES was developed, patients with antral G cell

hyperplasia being referred to as ZES type I, and those with the classical ZES (gastrinoma) were called ZES type II. However, this has not been universally accepted though it is easier to confirm the existence of a new syndrome than to refute it. It is evident, however, that the syndrome must be very rare. We have not seen such a case and Hansky (1974) found only three to conform to Ganguli's criteria among more than 400 patients with recurrent ulcer after surgery or peptic ulcer with hypergastrinaemia. There are several reasons which may account for this difficulty. The antral G cells have a patchy distribution, are often affected by local pathology such as gastritis (McFarland *et al.*, 1978b), and quantitative assessment of their number is difficult. In addition, there are wide variations between people in the gastrin content of the antrum (McFarland *et al.*, 1978b). We have been unable to find any clear cut differences in antral gastrin between patients with duodenal ulcer and non-ulcer dyspepsia, although a considerable increase in antral gastrin concentration has been shown in patients with pernicious anaemia.

The entity of G cell hyperplasia is appealing. If this condition were easy to diagnose it could lead to rational therapy for such patients, that is antrectomy. However, it is probably very rare.

GASTRIN DEFICIENCY

Pathological states associated with abnormalities of gut hormones are usually ascribed to excessive production of the hormone either from hyperplastic cells or from tumours. Seldom is a clinical condition ascribed to deficient production of the hormone, although this does not preclude the occurrence of such a deficiency. It is difficult to produce a clinical state of deficiency surgically because of the diffuse and widespread nature of this endocrine system. Recently, however, a patient with pernicious anaemia was found to have plasma gastrin levels within the normal range (McFarland *et al.*, 1978a) instead of the expected high levels. The patient had autoimmune disease with diabetes mellitus, and gastric parietal cell and thyroid antibodies. The gastrin response to a protein meal was subnormal and antral biopsy showed a normal histological appearance, but gastrin could not be shown in the biopsy material either by radioimmunoassay or by immunohistochemistry. We have been unable to determine whether this patient has autoantibodies directed towards the gastrin cells.

Secretin

Only a brief summary of the present status of secretin in physiology and pathology will be given

as it has not yet found an important place in clinical medicine.

Secretin was the first hormone to be described. In 1902, Bayliss and Starling found that when an extract of the upper intestinal mucosa was injected intravenously into anaesthetised dogs, the flow of pancreatic juice was stimulated. They concluded that an active substance was secreted from the duodenum into the blood stream to act subsequently on the exocrine pancreas, and they called it 'secretin'.

In 1966, Mutt and Jorpes described the amino-acid sequence of secretin, which is composed of 27 amino-acid residues and has structural similarities to glucagon, vasoactive intestinal peptide, and gastric inhibitory polypeptide.¹ It was synthesised by Bodansky *et al.* (1966). The hormone is present in both the duodenum and jejunum.

The development of a radioimmunoassay for secretin was somewhat delayed because of the lack of pure secretin. Antibodies to secretin are easily produced, but labelling of the hormone was difficult until the advent of synthetic secretin (Holohan *et al.*, 1973).

Secretin radioimmunoassays are highly specific and do not cross react with other known peptides. Most authors, using gel filtration and radioimmunoassays, have reported a single species of secretin in tissues but we have found a degree of heterogeneity in both tissues (Mason *et al.*, 1977) and plasma (Mason *et al.*, 1979). The reason for this discrepancy is not apparent though there have been some differences in the technique of immunopurification procedures. Differences in the nature of the antibodies are a possible explanation, but seem unlikely, as nearly all antibodies to secretin in our laboratory are directed towards the C terminal region of secretin, so that it is likely that the antisera used by other authors are also C terminal (Boden and Chey, 1973). Nevertheless, antibodies directed against other parts of the secretin molecule could account for differences between laboratories.

It appears likely that secretin has a physiological role in stimulating the exocrine pancreas to secrete a juice with a low enzyme content and a high bicarbonate content. The exocrine pancreas is exquisitely sensitive to small physiological doses of secretin given intravenously (Häcki *et al.*, 1977). Most would agree that secretin is released after instillation of acid into the duodenum (Boden *et al.*, 1974), but this may not represent a physiological stimulus. Chey *et al.* (1977) have reported that plasma secretin rises in the postprandial state in man, but others have been unable to show this (Boden, 1978). We ourselves, using a sensitive radioimmunoassay with a detection limit of 3 ng/l,

¹Glucose-dependent insulin-releasing polypeptide.

were unable to show rises in plasma secretin after the ingestion of a variety of oral stimuli including glucose, fat, protein, alcohol, hydrochloric acid, and a standard meal. However, Schaffalitzky de Muckadell and Fahrenkrug (1978) have shown that brief rises in plasma secretin concentration coincide with rapid falls in intraduodenal pH in the fasting state as well as postprandially. It seems possible, therefore, that such rapid fluctuations may account for the failure to show a rise in plasma secretin when measurements are made at arbitrary intervals. However, it is clear that plasma secretin does not rise after a meal to the same extent as other gut peptides, such as gastrin, gastric inhibitory polypeptide, insulin, pancreatic peptide, etc.

Because of the lack of rise of secretin after a meal and because secretin has lipolytic activity, we looked for a possible metabolic role. We found marked rises of plasma secretin during starvation in normal men (Henry *et al.*, 1975), though others have been unable to confirm this (Greenberg and Bloom, 1978). Subsequent studies in our laboratory have confirmed the original observation and shown that the secretin found in the plasma during starvation was identical with that found after a single overnight fast (Mason *et al.*, 1979).

Clearly there is insufficient evidence at present to define the role of secretin in physiology. There are some unsolved problems concerning the specificity of the radioimmunoassay, which require for their solution a similarly exhaustive approach as applied to the study of gastrin (see contribution by Professor Rehfeld, page 26).

THE ROLE OF SECRETIN IN PATHOLOGY

The secretion of secretin by a tumour has never been described. Therefore, the clinical and pathological changes that might be associated with excessive secretion of secretin are uncertain. Raised levels of circulating secretin have been reported in renal failure (Rhodes *et al.*, 1975b), but have not been confirmed by us (unpublished observations).

Impaired release of secretin in response to the ingestion or intraduodenal infusion of acid has been reported in coeliac disease (Rhodes *et al.*, 1975a; Bloom *et al.*, 1976; O'Connor *et al.*, 1977), and in patients with duodenal ulcer (Bloom and Ward, 1975), although the latter was not confirmed in more recent studies (Isenberg *et al.*, 1977; McLoughlin *et al.*, 1978).

Conclusion

Gastrin has a clear physiological role in acid secretion in man. It is implicated in several pathological states, but the most important of these is the

Zollinger-Ellison syndrome resulting from a gastrinoma. Radioimmunoassay of gastrin in plasma has been the most important advance in technology and has allowed a clearer definition of the role of gastrin in health and disease. Our own studies provide no evidence for the existence of a hypergastrinaemic subgroup of DU patients (without gastrinoma) and we recommend caution in the diagnosis of antral G cell hyperplasia. Plasma gastrin radioimmunoassay is an easy screening procedure for gastrinoma and its widespread application could result in considerable improvement in morbidity and mortality in this condition.

Although secretin may have been the first hormone to be described, its roles in physiology and pathology in man still await definition. Although it is released by intraduodenal acid, and although tiny physiological amounts given intravenously will stimulate the exocrine pancreas, it is only with great difficulty that rises of plasma secretin are detected after a meal. A considerable amount of controversy surrounds certain issues with respect to secretin and it is clearly required to define the specificity of secretin radioimmunoassays and also to establish the relationship of secretin in plasma to that in tissues.

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